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References: **1.** Kales J, *et al. Clin Pharmacol Ther 12* 691-697, Jul-Aug 1971 **2.** Kales A, *et al Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A, *et al. Clin Pharmacol Ther 19* 576-583, May 1976 **4.** Kales A, *et al. Clin Pharmacol Ther 32*:781-788, Dec 1982 **5.** Frost JD Jr, DeLucchi MR *J Am Geriatr Soc 27*:541-546, Dec 1979 **6.** Dement WC, *et al. Behav Med*, pp. 25-31, Oct 1978 **7.** Kales A, Kales JD. *J Clin Psychopharmacol 3*:140-150, Apr 1983 **8.** Tennont FS, *et al* Symposium on the Treatment of Sleep Disorders, Teleconference, Oct 16, 1984 **9.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21* 355-361, Mar 1977

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Contraindications: Known hypersensitivity to flurazepam HCl, pregnancy Benzodiazepines may cause fetal damage when administered during pregnancy Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patients to discontinue drug prior to becoming pregnant Consider the possibility of pregnancy prior to instituting therapy
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants An additive effect may occur if alcohol is consumed the day following use for nighttime sedation This potential may exist for several days following discontinuation Caution against hazardous occupations requiring complete mental alertness (*e g*, operating machinery, driving) Potential impairment of performance of such activities may occur the day following ingestion Not recommended for use in persons under 15 years of age Withdrawal symptoms rarely reported, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time Use caution in administering to addiction-prone individuals or those who might increase dosage
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia Consider potential additive effects with other hypnotics or CNS depressants Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported Also reported headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase, and paradoxical reactions, *e g*, excitement, stimulation and hyperactivity
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(ISSN 0093-0415/USPS 084 480) is published monthly for $30 per year (USA and Canada) by the California Medical Association, 44 Gough Street, San Francisco, CA 94103. Second-class postage paid at San Francisco, CA and additional mailing offices.
POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, P.O. Box 7602, San Francisco, CA 94120-7602.

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TRANDATE® 100

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Start your hypertensive patients with 100 mg b.i.d. and titrate upward as necessary*

- ☐ Reduces blood pressure in white *and* black patients[1]
- ☐ No significant effect on cardiac output,[2] serum lipids,[3,4] or renal blood flow[5]

Lipid regulation is not an indication for TRANDATE. Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia. Postural hypotension (2%) and rare instances of syncope have occurred.

*See **DOSAGE AND ADMINISTRATION** section of Brief Summary of Product Information on next page.

See next page for references and Brief Summary of Product Information.

Glaxo

TRANDATE® Tablets (labetalol hydrochloride) **BRIEF SUMMARY OF PRODUCT INFORMATION**

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labelalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labelalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labelalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor, therefore, use caution when administering labelalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia, it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labelalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labelalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm, therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labelalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the Maximum Recommended Human Dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labelalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting aloha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials comparing labetalol HCl, placebo, metoprolol, and propranolol over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose, as shown in the table below which depicts the entire US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related.

Labetalol HCl Daily Dose (mg)	200	300	400	600	800	900	1200	1600	2400
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesias	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature.

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus, positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps, toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, facial erythema, Peyronie's disease, reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat, laryngospasm; respiratory distress.

Hematologic: Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis, ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labelalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Overdosage with TRANDATE® Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain.

The following additional measures should be employed if necessary:

Excessive bradycardia—administer atropine (3 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and a diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dose is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1,200 to 2,400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered tid may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg bid.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labelalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of TRANDATE® Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, TRANDATE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44), and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43), and 500 (NDC 0173-0347-44), and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43), and 500 (NDC 0173-0348-44), and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F).

TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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The Western Journal of Medicine

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ISSN 0093-0415

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The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $4.50 (which includes postage and handling). Address all subscription communications to:
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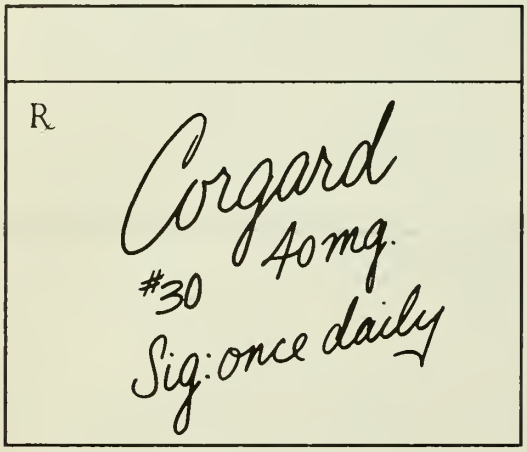

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DESCRIPTION: CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**— fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

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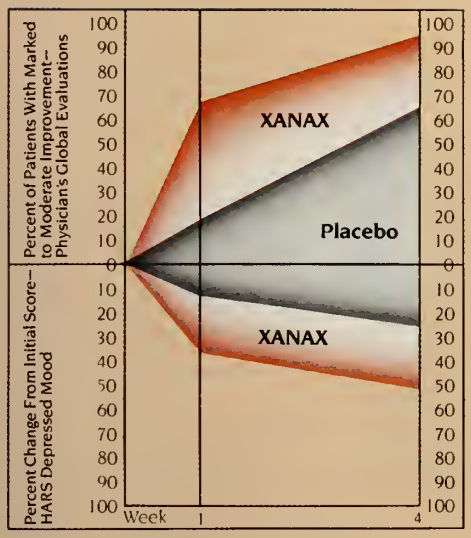

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1 Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients *Curr Ther Res* 1984;35(1):100-112.

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WARNINGS
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Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANTHOLOGY OF PLASTIC SURGERY—Edited by Harry Hayes, Jr, MD, Clinical Associate Professor of Surgery (Plastic), University of Arkansas for Medical Sciences, and Attending Surgeon, St Vincent Infirmary, Little Rock, Arkansas. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 333 pages, $55.

ATLAS OF CHEST WALL RECONSTRUCTION—Alan E. Seyfer, MD, Col, Medical Corps US Army, Chief, Plastic Surgery Service and Hand Surgery Section, Orthopaedic Surgery Service, Walter Reed Army Medical Center, Washington, DC, and Associate Professor of Surgery and Chief, Division of Plastic Surgery, Uniformed Services University of the Health Sciences; Geoffrey M. Graeber, MD, Lt Col, Medical Corps US Army, Thoracic Surgery Service, Walter Reed Army Medical Center and Chief, Department of Surgery, Walter Reed Army Institute of Research, Washington, DC, and Associate Professor of Surgery, Uniformed Services University of the Health Sciences, and Gary G. Wind, MD, Associate Professor of Surgery and Assistant Professor of Anatomy, Uniformed Services University of the Health Sciences, Bethesda, Maryland. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 251 pages, $98.

ATLAS OF THE HUMAN OOCYTE AND EARLY CONCEPTUS—Lucinda L. Veech, MLT, Director, Embryology Laboratory, Howard and Georgeanna Jones Institute for Reproductive Medicine, and Lecturer, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1986. 330 pages, $100.

BREATHING DISORDERS OF SLEEP—Volume 5 in Contemporary Issues in Pulmonary Disease—Edited by Norman H. Edelman, MD, Professor of Medicine and Physiology and Chief, Pulmonary Diseases Division, and Teodoro V. Santiago, MD, Professor of Medicine, Pulmonary Diseases Division, UMDNJ-Rutgers Medical School, New Brunswick, New Jersey. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 264 pages, $36.

CALIFORNIA HEALTH CARE LAW—Dan J. Tennenhouse, MD, JD, Medical-Legal Consultant and Lecturer, University of California, San Francisco, Schools of Medicine and Nursing, and Adjunct Professor, University of San Francisco School of Law. Contemporary Forums, 530 La Gonda Way, Suite E, Danville, CA 94526, 1985. 600 pages, $59.

CANCER OF THE FACE AND MOUTH—PATHOLOGY AND MANAGEMENT FOR SURGEONS—Ian A. McGregor, ChM, FRCS Glasg, FRCS Eng, Hon FRACS, Hon FRCSI, Hon FRCS Ed, President, Royal College of Physicians and Surgeons of Glasgow, and Director, West of Scotland Regional Plastic and Oral Surgery Unit, Canniesburn Hospital, Bearsden, Glasgow, and Frances M. McGregor, MB, FRCPath, Lecturer, University Department of Pathology, Royal Infirmary, Glasgow, Scotland. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 606 pages, $175.

CASARETT AND DOULL'S TOXICOLOGY—THE BASIC SCIENCE OF POISONS—Third Edition—Edited by Curtis D. Klaassen, PhD, Professor of Pharmacology and Toxicology, University of Kansas Medical Center; Mary O. Amdur, PhD, Senior Research Scientist, Energy Laboratory and Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, and Associate Professor of Toxicology, Harvard School of Public Health, Boston, and John Doull, MD, PhD, Professor of Pharmacology and Toxicology, University of Kansas Medical Center, Kansas City. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1986. 932 pages, $49.95.

COMPUTERS IN MEDICINE—Edited by Michael Anbar, PhD, Professor and Chairman of Biophysical Sciences, School of Medicine, State University of New York at Buffalo. Computer Science Press, Inc, 1803 Research Blvd, Rockville, MD 20850, 1986. 310 pages, $29.95.

CURRENT EMERGENCY THERAPY—Third Edition—Edited by Richard F. Edlich, MD, PhD, Distinguished Professor, Plastic Surgery and Biomedical Engineering, and Director, University of Virginia Burn Center, and Daniel A. Spyker, PhD, MD, Assistant Professor of Internal Medicine and Co-Director, Blue Ridge Poison Center, University of Virginia School of Medicine, Charlottesville. Aspen Publishers, Inc, 1600 Research Blvd, Rockville, MD 20850, 1986. 578 pages, $77.

DIAGNOSIS IS CANCER—A PSYCHOLOGICAL AND LEGAL RESOURCE HANDBOOK FOR CANCER PATIENTS, THEIR FAMILIES AND HELPING PROFESSIONALS—Edward J. Larschan, JD, PhD, and Richard J. Larschan, PhD. Bull Publishing Company, PO Box 208, Palo Alto, CA 94302, 1986. 126 pages, $9.95 (paperback).

DIAGNOSTIC BRONCHOSCOPY—A TEACHING MANUAL—Peter Stradling, MD(Lond), FRCP, FRPS, Lately Director of the Chest Clinic and Senior Lecturer in Respiratory Diseases, Royal Postgraduate Medical School, Hammersmith Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 180 pages, $75.

DRUG EVALUATIONS—6th Edition—Prepared by the American Medical Association, Department of Drugs and Technology, in cooperation with the American Society for Clinical Pharmacology and Therapeutics. AMA, Book & Pamphlet Fulfillment: OP-255/6, PO Box 10946, Chicago, IL 60610, 1986. 1,654 pages, $75 (20% discount for AMA members).

ETHICS IN EMERGENCY MEDICINE—Kenneth V. Iserson, MD, Associate Professor of Emergency Medicine (Surgery) and Residency Director in Emergency Medicine; Arthur G. Sanders, MD, Associate Professor of Emergency Medicine (Surgery) and Internal Medicine; Deborah R. Mathieu, PhD, Assistant Professor of Political Science, and Allen E. Buchanan, PhD, Professor of Philosophy, University of Arizona, Tucson. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1986. 277 pages, $39.50 (paperback).

GENERAL OPHTHALMOLOGY—11th Edition—Daniel Vaughan, MD, Clinical Professor of Ophthalmology, University of California, San Francisco, School of Medicine, and Taylor Asbury, MD, Clinical Professor of Ophthalmology, College of Medicine, University of Cincinnati. Appleton-Century-Crofts, 25 Van Zant St, East Norwalk, CT 06855, 1986. 396 pages, $22 (paperback).

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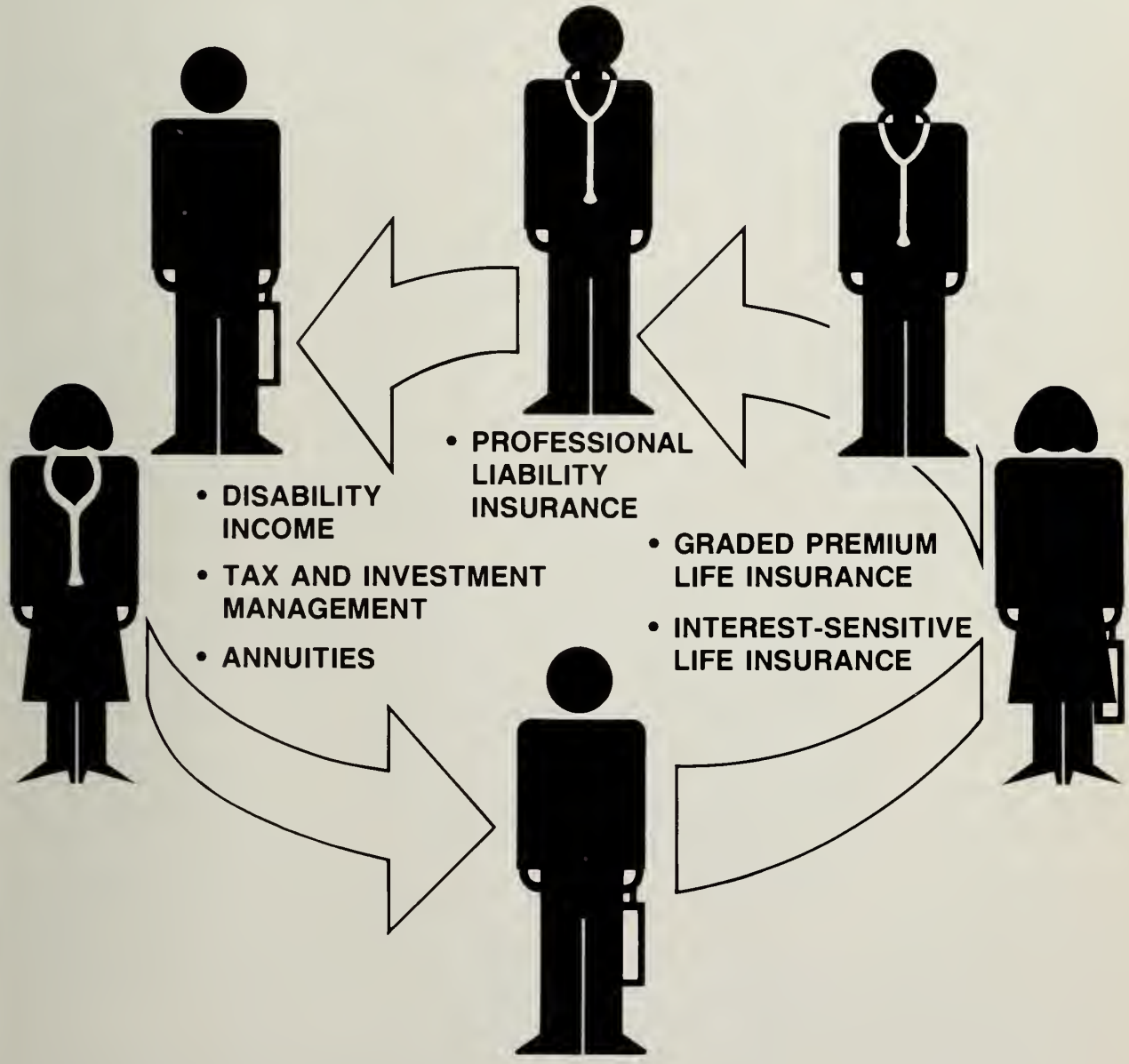

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 22-25—**Treatment Options in End Stage Cardiac Disease.** Loews Ventana Canyon Resort, Tucson. Thursday-Sunday. Contact: U of A.

February 2-7—**Emergency Care Update IX.** Monday-Saturday. Contact: U of A.

February 12-15—**Arizona Academy of Family Physicians Scientific Assembly—1987.** Scottsdale Hilton, Scottsdale. Thursday-Sunday. Contact AAFP, (602) 249-2021.

Feburary 13-15—**Anesthesia for the 80s.** La Paloma Resort, Tucson. Friday-Sunday. Contact: Beverly Richter for Arizona Society of Anesthesiologists, (602) 246-8901.

February 18—**Current Perspectives: Lipids.** Arizona Medical Association, Phoenix. Wednesday. Contact: ArMA.

February 18-21—**Crises and Controversies in Pediatrics.** Doubletree Inn, Tucson. Wednesday-Saturday. Contact: U of A.

February 19—**First Annual Interventional Angiography Symposium.** Thursday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

February 19-21—**Frontiers in Ophthalmology.** Thursday-Saturday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

February 22-25—**First Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Mountain Shadows Resort, Scottsdale. Sunday-Wednesday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

February 25-27—**Tenth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton, Scottsdale. Wednesday-Friday. Contact: Maricopa Medical Center, (602) 267-5444.

February 26-28—**Neurology and Neurosurgery of the Aging.** Mountain Shadows Resort, Scottsdale. Thursday-Saturday. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

March 4-8—**11th Annual Valley of the Sun Dermatologic Symposium.** Loews Paradise Valley Resort, Scottsdale. Wednesday-Sunday. Contact: Millard Thaler, MD, 2055 E Southern, #B, Tempe 85282.

March 11—**Current Perspectives: Lipids.** Pima County Medical Society Building, Tucson. Wednesday. Contact: ArMA.

March 11-13—**Them Ol' Bones.** Wednesday-Friday. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

March 17-20—**Pediatric Update—1987.** La Posada Resort, Scottsdale. Tuesday-Friday. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 19-21—**23rd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thursday-Saturday. Contact: Sandy Younker-Hellman, RN, U of A, (602) 327-5461.

March 19-21—**Gastroenterology for Clinicians.** Scottsdale. Thursday-Saturday. Contact: Jeanne Sun Harris, 4129 E Sandy Mt Rd, Scottsdale 85253.

March 21-22—**13th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Saturday-Sunday. Contact: Maricopa Medical Center, (602) 267-5371.

April 6-8—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Monday-Wednesday. Contact: American College of Cardiology, (301) 897-5400, ext 226.

April 22—**Current Perspectives: Wellness.** Arizona Medical Association, Phoenix. Wednesday. Contact: ArMA.

April 23—**Current Perspectives: Wellness.** VA Medical Center, Prescott. Thursday. Contact: ArMA.

April 24—**Clinical Aspect of Aging.** Friday. Contact: Dr Stonefeld, (602) 230-3479.

May 9-10—**Pathology of AIDS.** Loews Ventana Canyon Resort, Tucson. Saturday-Sunday. Contact: Beverly Richter for Arizona Society of Pathologists, (602) 246-8901.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

February 11-14—**Immunology and the Clinical Practice of Allergy.** UCSD at San Diego Hilton Beach and Tennis Resort. Wednesday-Saturday. 20 hrs. Contact: UCSD

March 18-21—**10th Annual Course: Frontiers in Allergy and Asthma—A Comprehensive Update for the Treatment of Allergy/Asthma Patients.** UCD at Embassy Suites, Napa Valley. Wednesday-Saturday. 17 hrs. Fee: $225. Contact: UCD.

ANESTHESIOLOGY

January 30—February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

(Continued on Page 23)

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Please consult Brief Summary of Prescribing Information on the following page.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**)
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min, second- and third-degree heart block, significant first-degree heart block (P-R interval ≥ 0 24 sec); systolic blood pressure < 100 mmHg or moderate-to-severe cardiac failure (see **WARNINGS**)

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously Both digitalis and Lopressor slow AV conduction
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic The response should be observed closely If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken Patients should be warned against interruption or discontinuation of therapy without the physician's advice Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures
Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers
Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e g , tachycardia) of hyperthyroidism Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure
During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued
Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered
AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0 26 sec), second-, or third-degree heart block Acute myocardial infarction also produces heart block
If heart block occurs, Lopressor should be discontinued and atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered
Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above)
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician
Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs, (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e g , reserpine) may have an additive effect when given with beta-blocking agents Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia Neither finding represents symptoms of a known disease entity in man In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor
All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative
No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55 5 times the maximum daily human dose of 450 mg
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55 5 times the maximum daily human dose of 450 mg Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal These studies have revealed no evidence of impaired fertility or teratogenicity There are no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug Caution should be exercised when Lopressor is administered to a nursing woman
Pediatric Use
Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients Depression has been reported in about 5 of 100 patients Mental confusion and short-term memory loss have been reported Headache, nightmares, and insomnia have also been reported
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients Cold extremities, arterial insufficiency, usually of the Raynaud type, palpitations, congestive heart failure, peripheral edema, and hypotension have been reported in about 1 of 100 patients (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**)
Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients
Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients Worsening of psoriasis has also been reported
Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients Musculoskeletal pain, blurred vision, and tinnitus have also been reported.
There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes Discontinuation of the drug should be considered if any such reaction is not otherwise explicable
The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear
Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27 4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15 9%	6.7%
Second- or third-degree heart block	4.7%	4 7%
First-degree heart block (P-R ≥ 0 26 sec)	5.3%	1 9%
Heart failure	27.5%	29 6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients
Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.
Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor
Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**)
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death
Oral LD_{50}'s (mg/kg): mice, 1158-2460, rats, 3090-4670
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure
Treatment
There is no specific antidote
In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**)
On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed
Elimination of the Drug: Gastric lavage should be performed
Bradycardia: Atropine should be administered It there is no response to vagal blockade, isoproterenol should be administered cautiously
Hypotension: A vasopressor should be administered, e g , levarterenol or dopamine
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered
Cardiac Failure: A digitalis glycoside and diuretic should be administered In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

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Heals active duodenal ulcers after 4 weeks in most patients*[1]

ZANTAC 300 mg h.s.	*270/320*	*84%*
ZANTAC 150 mg b.i.d.	*292/345*	*85%*

In well-controlled, double-blind, multicenter trials, ZANTAC 300 mg h.s. healed active duodenal ulcers in 84% of patients after 4 weeks. After 8 weeks, healing rates may be higher with ZANTAC 150 mg b.i.d. (92%) than with ZANTAC 300 mg h.s. (87%).

Relieves pain and other symptoms as effectively as ZANTAC 150 mg b.i.d.[1]

Zantac® 300

ranitidine HCl/Glaxo 300 mg tablets

Once-daily dosing may enhance compliance in patients for whom dosing convenience is important

Side-effects profile comparable to ZANTAC 150 mg b.i.d.[1-3]

Headache—sometimes severe—has been reported. Rare effects on the CNS, cardiovascular, GI, hepatic, and integumental systems have been observed, as well as rare cases of hypersensitivity reactions. See ADVERSE REACTIONS section of Brief Summary of Product Information before prescribing.

No significant interference with the hepatic cytochrome P-450 enzyme system at recommended doses

ZANTAC 300 mg h.s. had no significant drug interactions with theophylline or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications which decrease gastric acidity are administered.

It is not known exactly how much acid inhibition is needed to heal ulcers.

Glaxo / ROCHE

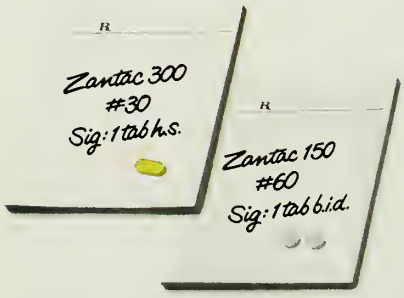
See next page for references and Brief Summary of Product Information.

IN ACTIVE DUODENAL ULCERS

Once-a-night h.s. therapy controls acid rain

Zantac® 300
ranitidine HCl/Glaxo 300 mg tablets

Two effective regimens to treat active duodenal ulcers:



References: **1.** Data available on request, Glaxo Inc. **2.** Ireland A, Colin-Jones DG, Gear P, et al: Ranitidine 150 mg twice daily vs 300 mg nightly in treatment of duodenal ulcers. *Lancet* 1984;2:274-275. **3.** Colin-Jones DG, Ireland A, Gear P, et al: Reducing overnight secretion of acid to heal duodenal ulcers. *Am J Med* 1984;77 (suppl 5B):116-122.

ZANTAC® 150 Tablets (ranitidine hydrochloride)
ZANTAC® 300 Tablets (ranitidine hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function. Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Although recommended doses of ZANTAC do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Lack of experience to date precludes recommending ZANTAC for use in children or pregnant patients. Since ZANTAC is secreted in human milk, caution should be exercised when administered to a nursing mother.

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to ZANTAC® administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

In normal volunteers, SGPT values were increased to at lea twice the pretreatment levels in 6 of 12 subjects receiving 100 m qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qi for five days. With oral administration there have been occasion reports of reversible hepatitis, hepatocellular or hepatocanalic lar or mixed, with or without jaundice.

There have been rare reports of reversible leukopenia, granul cytopenia, thrombocytopenia, and pancytopenia.

Although controlled studies have shown no antiandrogeni activity, occasional cases of gynecomastia, impotence, and loss libido have been reported in male patients receiving ZANTAC, b the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild eryt ema multiforme, and, rarely, alopecia, have been reported, as we as rare cases of hypersensitivity reactions (eg, bronchospasm fever, rash, eosinophilia) and small increases in serum creatinin

OVERDOSAGE: Information concerning possible overdosage and i treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: **Active Duodenal Ulcer:** The curre recommended adult oral dosage is 150 mg twice daily. An alte nate dosage of 300 mg once daily at bedtime can be used f patients in whom dosing convenience is important. The adva tages of one treatment regimen compared to the other in a partic lar patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosag is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellis Syndrome): The current recommended adult oral dosage is 150 m twice a day. In some patients it may be necessary to admini ZANTAC 150-mg doses more frequently. Doses should be adjust to individual patient needs, and should continue as long as cli cally indicated. Doses up to 6 g/day have been employed patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosag is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 m twice a day.

See full prescribing information for dosage adjustment f patients with impaired renal function.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochlori equivalent to 300 mg of ranitidine) are yellow, capsule-shape tablets embossed with "ZANTAC 300" on one side and "Glaxo" o the other. They are available in bottles of 30 (NDC 0173-0393-4 and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent t 150 mg of ranitidine) are white tablets embossed with "ZANTA 150" on one side and "Glaxo" on the other. They are available bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Prote from light. Replace cap securely after each opening.

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Glaxo Inc.
Research Triangle Park, NC 27709

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(Continued from Page 16)

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: Ohio State University Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. Contact: UCSF.

March 21-22—**Los Angeles County Society of Anesthesiologists 32nd Postgraduate Assembly.** Los Angeles Hilton Hotel. Saturday-Sunday. Contact: LA County Society of Anesthesiologists, 333 S Beverly Dr, Ste 111, Beverly Hills 90212. (213) 556-8865.

April 27-May 1—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Kauai Hotel, Poipu Beach, Hawaii. Monday-Friday. 20 hrs. Contact: Linda P. Londerville, CSA, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

June 25-28—**California Society of Anesthesiologists Annual Meeting.** Hotel Inter-Continental, San Diego. Thursday-Sunday. 13 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

February 16-18—**Clinical Hematology and Oncology—1987.** Scripps Clinic, La Jolla at Vacation Village Resort, San Diego. Monday-Wednesday. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 28—**Colorectal Carcinoma—1987.** Hospital of the Good Samaritan at Moseley-Salvatori Conference Center, Los Angeles. Saturday. 5 hrs. Fee: $110. Contact: Ilona Kapay-Carlos, 616 S Witmer St, Los Angeles 90017. (213) 977-2429.

March 7—**Supportive Care of the Cancer Patient.** UCI at Long Beach. Saturday. 6 hrs. Contact: UCI.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Associate Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

March 12-14—**2nd International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Saturday. 20 hrs. Contact: UCSD.

March 18-20—**7th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 18 hrs. Fee: $275-325. Contact: UCSF

April 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Newporter Hotel, Newport Beach. Sunday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 1—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Vacation Village Resort, San Diego. Friday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

CARDIOLOGY

January 23-25—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

January 29-31—**Cardiology '87.** Scripps Memorial Hospital, La Jolla at La Jolla Marriott Hotel, San Diego. Thursday-Saturday. 18 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 29-31—**Clinical Nuclear Cardiology: Case Review with the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thursday-Saturday. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400.

February 4-7—**4th Annual Cardiopulmonary Conference.** American College of Chest Physicians at Lake Tahoe. Wednesday-Saturday. Contact: ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200 or (916) 739-8833.

February 5-8—**Pathophysiology and Techniques of Cardiopulmonary Bypass: VII.** Cardiothoracic Research and Education Foundation at Sheraton Island East Hotel, San Diego. Thursday-Sunday. 15 hrs. Fee: $300. Contact: CREF, PO Box 33185, San Diego 92103. (619) 692-9115.

February 6-7—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

February 9-13—**2nd Annual Cardiovascular Conference.** American College of Cardiology at Sheraton Royal Waikaloa Hotel, Kohala Coast, Hawaii. Monday-Friday. 20 hrs. Fee: $470. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 227.

February 11—**Cardiology.** Enloe Hospital, Chico. Wednesday. 7 hrs. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

February 13-14—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Americana Resort Hotel, Palm Springs. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

February 18—**2nd Annual Current Concepts in the Mechanisms and Treatment of Cardiac Arrythmias.** Daniel Freeman Memorial Hospital, Inglewood. Wednesday. 6 hrs. Contact: Daniel Freeman Memorial Hospital, 333 N Prairie Ave, Inglewood 90301. (213) 674-7050, ext 3427.

March 22-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Royal Lahaina Hotel, Maui, Hawaii. Sunday-Wednesday. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 27-28—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 10-11—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Inter-Continental Hotel, San Diego. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 27-May 6—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn, Rancho Santa Fe. Monday-Wednesday. 40 hrs. Fee: $800. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 1-2—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Friday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in CO 798-9682.

June 7-10—**Critical Examination Review Course.** American College of Chest Physicians at Hotel Del Coronado, Coronado. Sunday-Wednesday. 30 hrs. Fee: $575. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (312) 698-2200.

June 10—**Cardiology: Arrhythmias.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wednesday-Saturday. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 18-20—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Waikiki Hotel, Honolulu, Hawaii. Thursday-Saturday. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 25-27—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Hotel, Costa Mesa. Thursday-Saturday. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

DERMATOLOGY

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates, San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 13-14—**Cutaneous Laser Surgery.** Good Samaritan Hospital at Sheraton Harbor Island, San Diego. Friday-Saturday. Contact: Paul D. Indman, MD, 15195 National Ave, Ste 201, Los Gatos 95030. (408) 358-2788.

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Friday-Saturday. 11 hrs. Contact: UCLA.

EMERGENCY MEDICINE

February 2-4—**Trauma Management—1987.** UCSD at Hotel Inter-Continental, San Diego. Monday-Wednesday. 20 hrs. Contact: UCSD.

February 22-27—**10th Annual UCD Winter Conference: Emergency Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 27 hrs. Fee: $395. Contact: UCD.

February 28—**Major and Minor Hand Problems in the Emergency Department.** UCSF at UCSF. Saturday. 7 hrs. Contact: UCSF.

March 8-13—**8th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 20 hrs. Fee: $350. Contact: Medical Conferences, Inc, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Laboratory.** UCSD. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

April 11-18—**Infectious and Toxicologic Emergencies.** Scripps Memorial Hospital, Encinitas at Waiohai Resort and Poipu Beach Hotel, Kauai, HI. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 25-May 1—**Critical Care Medicine.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. Saturday-Friday. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

May 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians—Symposium I and Advanced Emergency Procedures Laboratory.** UCSD at Hotel Inter-Continental, San Diego. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

May 13-17—**9th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wednesday-Sunday. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

June 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III and Advanced Emergency Procedures Lab.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 32 hrs. Fee: $325-440. Contact: UCSD.

INTERNAL MEDICINE

January 29-31—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Grand Hotel, San Diego. Thursday-Saturday. 18 hrs. Contact: Shirley Kolkey, UCSD, (619) 294-5339.

January 30-31—**Update on Uses of Lasers in Urology.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

January 31—**Rapid Viral Diagnosis.** UCLA at Westwood. Saturday. 7 hrs. Fee: $100. Contact: UCLA.

January 31-February 7—**Infectious Disease in General Medical and Pediatric Practice.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. One week. 24 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

February 1-5—**Internal Medicine 1987: An Office Practice Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Sunday-Thursday. 28 hrs. Fee: $395. Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 1-6—**Winter Urologic Forum.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 22 hrs. Fee: $370. Contact: UCD.

February 4-6—**Emerging Technology and Future Trends in Clinical Laboratory Molecular Analyses.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Wednesday-Friday. 20 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, Box 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 8-13—**General Internal Medicine: Concepts and Controversies.** UCSF at Hyatt Lake Tahoe, Nevada. Sunday-Friday. Contact: UCSF

February 11-13—**20th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. 15 hrs. Contact: UCSF.

February 13-14—**5th Annual Infectious Disease: New Information for Managing Infection.** UCD at Sheraton Sunrise Hotel, Sacramento. Friday-Saturday. 9 hrs. Fee: $145. Contact: UCD.

February 19-21—**Advances in the Management of Infectious Disease.** University of Michigan at Kahala Hilton Hotel, Honolulu, Hawaii. Thursday-Saturday. 11.75 hrs. Fee: $285. Contact: Gayle Fox, Office of CME, Univ of Michigan, Towsley Center, Box 0201, Ann Arbor, Michigan 48109-0201. (313) 763-1400.

March 6-7—**Current Topics in Diagnosis and Therapy of Infectious Diseases.** American College of Physicians at Santa Barbara. Friday-Saturday. Contact: Registration Services, ACP, 4200 Pine St, Philadelphia, PA 19104. (800) 523-1546 or (215) 243-1200.

March 7-14—**Topics in Internal Medicine for Primary Care Physicians.** University of Colorado at Molokai Sheraton, Molokai, Hawaii. One week. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

March 11—**Rheumatology: Osteoarthritis and Nonsteroidal Drugs.** LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

March 30-April 1—**Federation of Western Societies of Neurological Science 24th Annual Meeting.** Monday-Wednesday at Hotel Del

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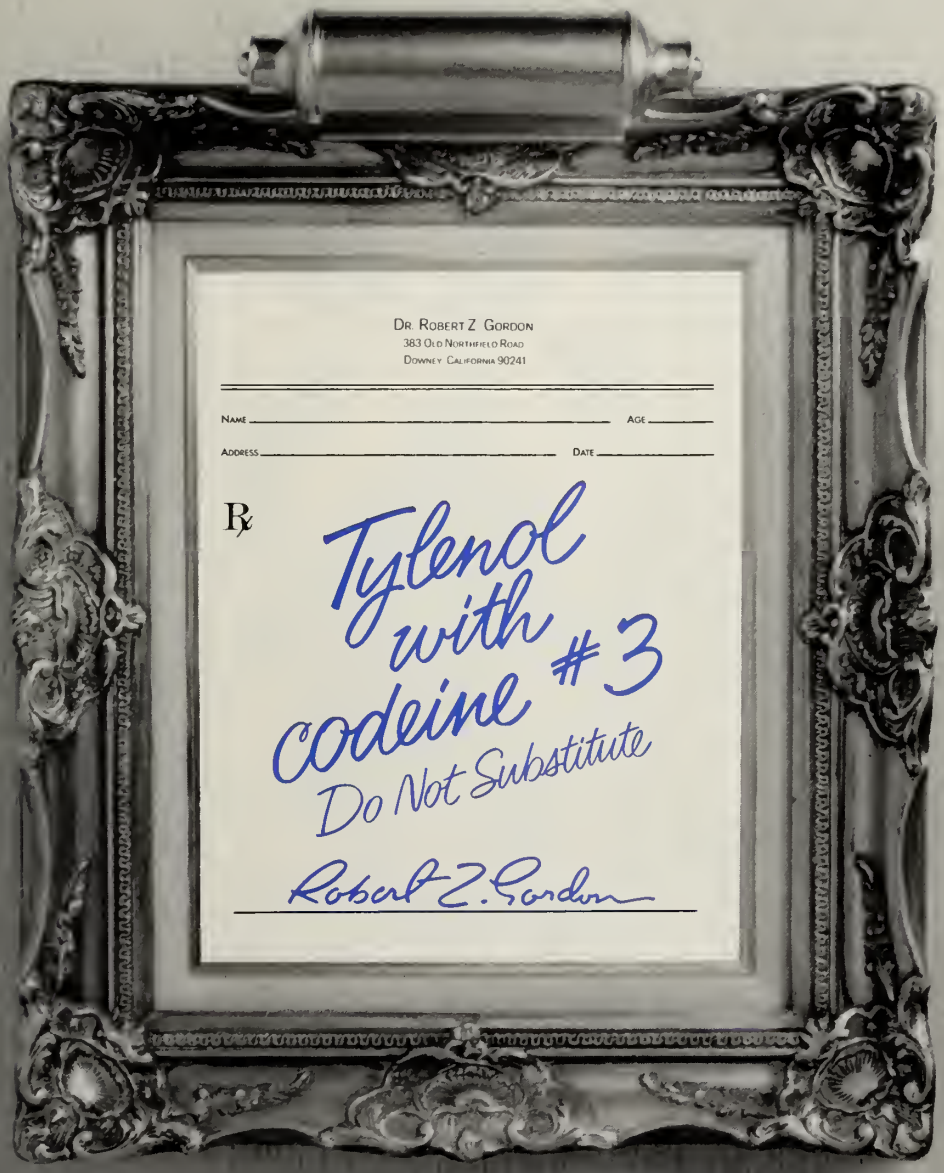

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with codeine phosphate

TABLETS Ⓒ III ELIXIR Ⓒ V

Tablets: Contain Codeine Phosphate*: No. 3—30 mg; No. 4—60 mg—plus Acetaminophen 300 mg.
Elixir: Each 5 mL contains 12 mg Codeine Phosphate* plus 120 mg Acetaminophen (Alcohol 7%).
*Warning: May be habit forming.

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E. R. W. FOX, MD
Dr Fox is in private practice in Coeur d'Alene, Idaho, and is the Special Editor for Idaho.

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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When it's allergic rhinitis

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INDICATIONS: NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.

CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.

PRECAUTIONS:

General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy.

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients.

One patient in the clinical trials developed anaphylaxis.

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

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Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

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References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)" and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

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(Continued from Page 24)

Coronado, Coronado. Contact: Patrick D. Lyden, MD, Dept of Neurosciences, UCSD Medical Center H-815A, 225 W Dickinson St, San Diego 92103. (619) 452-3940.

April 8-10—**Advances in Infectious Disease: Current Therapy.** UCSF at Hyatt Regency Embarcadero, San Francisco. Wednesday-Friday. 16 hrs. Fee: $350. Contact: UCSF.

April 23-24—**7th Annual Infectious Diseases—Clinical Update.** Sutter Community Hospitals and Mercy Hospital of Sacramento at Red Lion Inn, Sacramento. Thursday-Friday. 14 hrs. Contact: Infectious Diseases Symposium, Metro Centre, 1600 Sacramento Inn Way, Ste 132, Sacramento 95815. (916) 925-1366.

May 2—**New Treatments in Liver and Biliary Tract Disease.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 7 hrs. Fee: $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 16—**Clinical Aspects of Viral Disease.** Grossmont District Hospital at Kona Kai Club, San Diego. Saturday. Contact: Vera Belyeu, Grossmont District Hospital, 5555 Grossmont Center Dr, La Mesa 92041. (619) 465-0711, ext 245.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 32 hrs. Fee: $440. Contact: UCSF.

June 17-19—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt on Union Square. San Francisco. Wednesday-Friday. Fee: $375. Contact: UCSF.

June 22-26—**Advances in Internal Medicine.** UCSF at UCSF. Monday-Friday. 32 hrs. Fee: $440.

OB/GYN

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 17—**OB/GYN Pathology II.** USC at Pasadena Hilton Hotel. Saturday. 6.25 hrs. Fee: $105. Contact: USC.

February 1-5—**OB/GYN Update—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Thursday. Contact: UCD.

February 7-13—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Hawaii. Saturday-Friday. 23 hrs. Fee: $525. Contact: USC.

February 8-12—**15th Obstetric Anesthesia Conference.** Ohio State University Hospital at Sheraton Waikiki Hotel, Hawaii. Sunday-Thursday. Contact: OSU Hospital, Dept of Anesthesiology, 410 W 10th Ave, Columbus, OH 43210. (614) 421-8487.

February 11-12—**Basic Colposcopy.** Good Samaritan Hospital at Sheraton Harbor Island, San Diego. Wednesday-Thursday. Contact: Paul D. Indman, MD, 15195 National Ave, Ste 201, Los Gatos 95030. (408) 358-2788.

February 11-12—**Advanced Colposcopy.** Good Samaritan Hospital at Sheraton Harbor Island, San Diego. Wednesday-Thursday. Contact: Paul D. Indman, MD, 15195 National Ave, Ste 201, Los Gatos 95030. (408) 358-2788.

February 11-12—**Gynecologic Laser Surgery.** Good Samaritan Hospital at Sheraton Harbor Island, San Diego. Wednesday-Thursday. Contact: Paul D. Indman, MD, 15195 National Ave, Ste 201, Los Gatos 95030. (408) 358-2788.

February 12-17—**42nd Annual Postgraduate OB/GYN Assembly of Southern California Hills.** Thursday-Tuesday. 28 hrs. Contact: OB/GYN Assembly of Southern California Hills, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 21—**Infertility Update IV.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Friday-Sunday. Contact: UCSF.

March 25-28—**Gynecological Surgery With Emphasis on Vulvar and Vaginal Disease.** UCI at Hilton Riviera, Palm Springs. Wednesday-Saturday. 16.5 hrs. Contact: UCI.

April 2-4—**Fetal Diagnosis and Treatment.** UCSD. Thursday-Saturday. Contact: UCSD.

April 30-May 2—**12th Annual Symposium: Care of the Sick Newborn.** UCI. Thursday-Saturday. Contact: UCI.

May 6-10—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Americana Canyon Hotel, Palm Springs. Wednesday-Sunday. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

June 11-13—**Gynecologic Oncology and Breast Disease.** American College of Obstetricians and Gynecologists at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: Robin Murray, ACOG, 600 Maryland Ave, SW, Washington, DC 20024-2588. (202) 638-5577.

June 30-July 5—**5th Annual Controversies in Obstetrics and Gynecology.** UCI at Mauna Kea Beach Resort, Hawaii. Tuesday-Sunday. Contact: UCI.

OPHTHALMOLOGY

January 22-23—**YAG Laser Update—1987.** UCSD at Hotel Inter-Continental, San Diego. Thursday-Friday. Contact: Bonnie Sanderson, UCSD, (619) 294-5840.

February 27-28—**Current Surgical Treatment for Myopia with Special Concentration in Scleral Reinforcement.** San Gabriel Valley Medical Center. Friday-Saturday. 11 hrs. Fee: $275-325. Contact: Karen Frankfurt, Thompson Eye Foundation, 416 Las Tunas Dr, #102, San Gabriel 91776. (818) 289-7858.

ORTHOPAEDICS

January 21—**American Orthopaedic Society for Sports Medicine Meeting.** Moscone Center, San Francisco. Wednesday. 7.5 hrs. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

February 13-14—**Medical and Orthopedic Problems in Sports Medicine.** UCI at Irvine Hilton Hotel. Friday-Saturday. 11 hrs. Fee: $95. Contact: J. Massimino, MD, 896 Town and Country Office Park, Orange 92668. (818) 989-3432.

April 3-5—**Techniques of Intramedullary Nailing: Tibia, Humerus, and Femur.** Centinela Hospital Medical Center at Century Plaza Hotel, Century City. Friday-Sunday. 15 hrs. Fee: $395. Contact: Jeanne Spala, DME, Centinela Hospital, 555 E Hardy St, Inglewood 90307. (213) 673-4660, ext 8213.

April 30-May 2—**American Back Society Spring Symposium on Back Pain.** Anaheim Hilton Hotel. Thursday-Saturday. Contact: Aubrey A. Swartz, MD, American Back Society, 2647 E 14th St, Oakland 94601. (415) 536-9929.

May 4-8—**Osteoporosis/Spine Update.** UCSF at Hyatt Regency Hotel, San Francisco. Monday-Friday. Contact: UCSF.

PATHOLOGY

January 17—**OB/GYN Pathology II.** USC at Pasadena Hilton Hotel. Saturday. 6.25 hrs. Fee: $105.

May 21-22—**Annual Meeting: Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thursday-Friday. 12 hrs. Contact: UCSF.

PEDIATRICS

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

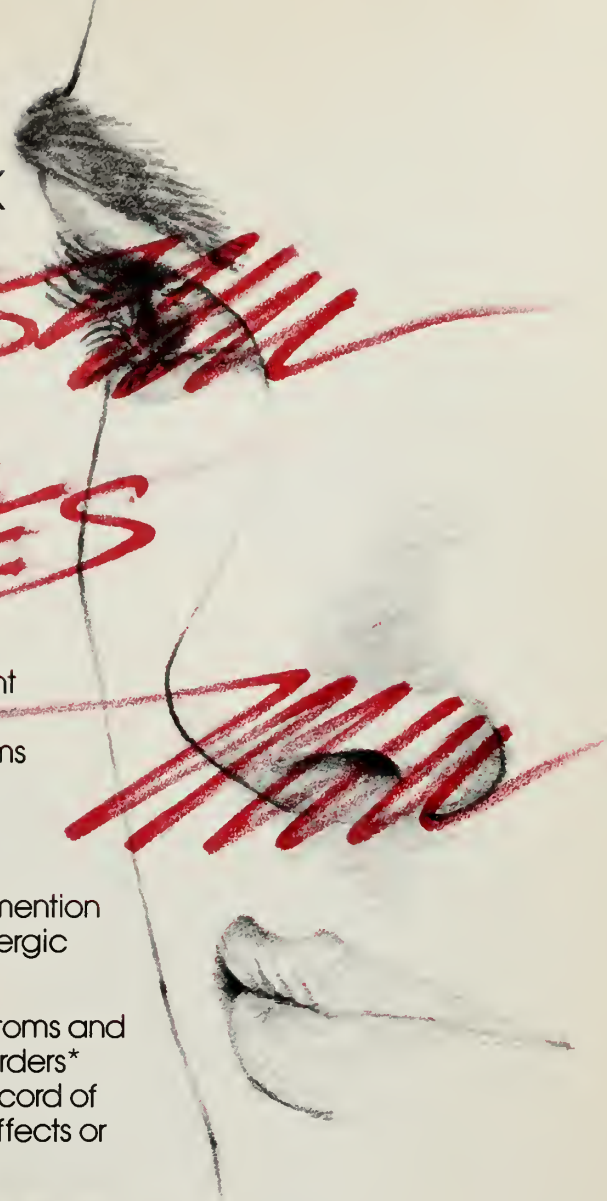
January 24-31—**Pediatric Emergencies.** Scripps Memorial Hospital, Encinitas at Kona Surf Resort, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein/AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 25-28—**12th Annual Winter Ski and Study Program.** American Academy of Pediatrics at Caesars Tahoe Hotel, Lake Tahoe, Nevada. Sunday-Wednesday. 10 hrs. Fee: $250. Contact: AAP, Chptr 2, PO Box 2134, Inglewood 90305. (213) 757-1198.

January 30-February 1—**25th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Marriott Hotel. Friday-Sunday. 15 hrs. Fee: $175. Contact: Wayne Herbert, MD, Children's Hospital of Los Angeles, PO Box 54700, Los Angeles 90054. (213) 669-2262.

(Continued on Page 36)

DON'T OVERLOOK THE EYES WHEN TREATING ALLERGIES



More than 8 out of 10 patients who present with allergic rhinitis may suffer from concurrent allergic ocular signs and symptoms —itchy, scratchy eyes, erythema and edema, tearing, irritation—according to two recent studies.[1,2]

What's worse is that many patients don't mention their ocular symptoms when reporting allergic rhinitis unless specifically asked.

So look for the overlapping clinical symptoms and then confidently treat allergic ocular disorders* with OPTICROM. It has a proven clinical record of efficacy with freedom from serious side effects or ocular toxicity.

OPHTHALMIC SOLUTION

OPTICROM® 4%

(cromolyn sodium, USP)

THE SOLUTION FOR ALLERGIC OCULAR DISORDERS*

Reference 1,2. Data on file, Fisons Corporation
Independent Studies by DTW Market Research Group July 1985.

*See below for listing of certain allergic ocular disorders

INDICATIONS AND USAGE: OPTICROM is indicated in the treatment of certain allergic ocular disorders referred to by the terms vernal keratoconjunctivitis, vernal conjunctivitis, giant papillary conjunctivitis, vernal keratitis, and allergic keratoconjunctivitis. The etiologic factors are unknown, but common airborne allergens and contact lenses have been implicated.[1]

Symptomatic response to therapy (decreased itching, tearing, redness, and discharge) is usually evident within a few days, but longer treatment for up to six weeks is sometimes required. Once symptomatic improvement has been established, therapy should be continued for as long as needed to sustain improvement.

If required, corticosteroids may be used concomitantly with OPTICROM.

Users of soft (hydrophilic) contact lenses should refrain from wearing lenses while under treatment with OPTICROM (see **Contraindications**). Wear can be resumed within a few hours after discontinuation of the drug.

CONTRAINDICATIONS: OPTICROM is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or to any of the other ingredients.

As with all ophthalmic preparations containing benzalkonium chloride, patients are advised not to wear soft contact lenses during treatment with OPTICROM.

PRECAUTIONS: General: Patients may experience a transient stinging or burning sensation following application of OPTICROM.

The recommended frequency of administration should not be exceeded. The dose for adults and children is 1-2 drops in each eye 4-6 times a day at regular intervals.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by six months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when OPTICROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 4 years have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reaction attributed to the use of OPTICROM, on the basis of reoccurrence following readministration, is transient ocular stinging or burning upon instillation.

The following adverse reactions have been reported as infrequent events. It is unclear whether they are attributable to the drug: conjunctival injection, watery eyes, itchy eyes, dryness around the eye, puffy eyes, eye irritation, styes.

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCE: 1. Allansmith MR, Abelson MB. Ocular Allergies. In: *The Cornea*, ed. by G. Smolin, RA Thoft, Little, Brown and Co., Boston/Toronto, 1983: 231-43.

See package insert for full prescribing information.

OPTICROM® is a registered trademark of Fisons plc.
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Motrin® 800 mg TABLETS

ibuprofen

a stronger reason to prescribe Motrin Tablets

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Motrin® 800 mg TABLETS
ibuprofen

Extra-Strength Motrin Tablets— a convenient way to tap the full potential of Motrin:

The newest strength of *Motrin* Tablets

makes treatment easier for arthritis patients who need the doses that provide higher levels of anti-inflammatory activity as well as potent analgesia...just 1 tablet t.i.d. provides 2400 mg/day.

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Please see adjacent page for a brief summary of prescribing information.

Upjohn 100 A Century of Caring 1886·1986

MOTRIN® Tablets
(ibuprofen)

CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAIO's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAIO's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAIO therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MDTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship*

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown*

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

HOW SUPPLIED:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
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Unit-dose package of 100	Unit-dose package of 100	Bottles of 500
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CONTINUING MEDICAL EDUCATION

(Continued from Page 32)

February 3-8—**16th Annual Pediatric Postgraduate Course: Pediatric Update 1987.** Schneider Children's Hospital of Long Island Jewish Medical Center, Rancho Las Palmas, Palm Springs. Tuesday-Sunday. Contact: Ann J. Boehme, Schneider Children's Hospital of Long Island Jewish Medical Center, New Hyde Park, NY 11042. (718) 470-8650.

February 5-7—**Current Concepts in Pediatric Medicine.** American Academy of Pediatrics at Holiday Inn Embarcadero, San Diego. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, AAP, Division of Continuing Education, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

February 12-13—**2nd Annual Pediatric Intesive Care Symposium.** UCI at Sheraton Newport Hotel, Newport Beach. Thursday-Friday. Contact: UCI.

February 16-18—**Pediatrics Update 1987.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Monday-Wednesday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 5-7—**Advances in Pediatrics II.** American Academy of Pediatrics at Kauai, Hawaii. Thursday-Saturday. 16 hrs. Fee: $330. Contact: Neal A. Baker, Div of Continuing Education, AAP, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

March 12-15—**17th Annual Combined Socal Pediatric Postgraduate Meeting.** American Academy of Pediatrics at Desert Princess Hotel, Palm Springs. Thursday-Sunday. Contact: AAP, PO Box 2134, Inglewood 90305. (213) 757-1198.

April 2-4—**20th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

April 8—**Pediatrics: Genetics.** LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

PSYCHIATRY

January 25-30—**13th Annual Midwinter Program for Psychiatrists: Special Focus on Adolescent Psychiatry.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 25 hrs. Fee: $355-415. Contact: UCD.

March 28-29—**The Cutting Edge 1987: Difficult Treatment Problems With Borderline and Narcissistic Patients.** UCSD at Hotel Inter-Continental, San Diego. Saturday-Sunday. 13 hrs. Contact: UCSD.

April 10-11—**Mental Health in the Workplace.** UCSF at Cathedral Hill Hotel, San Francisco. Friday-Saturday. 11.5 hrs. Fee: $200. Contact: UCSF.

RADIOLOGY

January 22-24—**Duplex Imaging.** UCSD at San Diego Hilton Beach and Tennis Resort. Thursday-Saturday. 18.5 hrs. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113/ (404) 641-9773.

January 30-February 1—**10th Annual Evoked Potential and Electrodiagnostic Workshop.** UCI. Friday-Sunday. 20 hrs. Contact: UCI.

January 30-February 1—**39th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 21 hrs. Fee: $350. Contact: Diane L. Johnson, Los Angeles Radiological Society, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

February 2-6—**Radiology: Imaging and Intervention.** UCSD at Hotel Inter-Continental, San Diego. Monday-Friday. 21.5 hrs. Fee: $425. Contact: Dawn Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

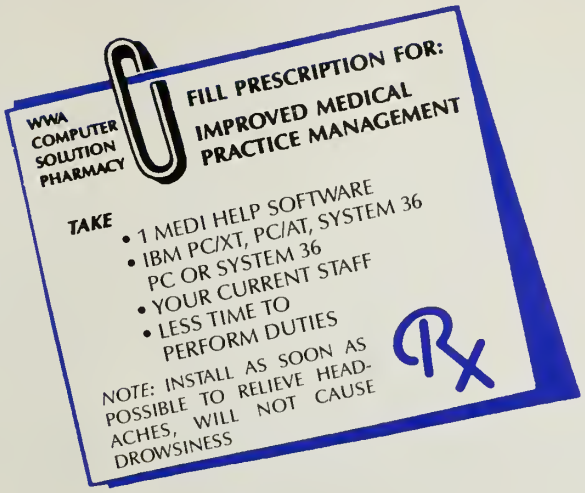
February 2-7—**6th Annual UCSD Imaging and Intervention Conference.** Inter-Continental Hotel, San Diego. Monday-Saturday. 21.5 hrs. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

February 3-7—**13th Annual Midwinter Radiological Post Conference Seminar.** Los Angeles Radiological Society at Hyatt Regency, Kaanapali, Maui, Hawaii. Tuesday-Saturday. 18 hrs. Fee: $375. Contact: LARS-MWRC, PO BOX 91215, Los Angeles 90009-1215. (213) 642-0921.

February 11—**Interventional Radiology.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

(Continued on Page 121)

JUST WHAT THE DOCTOR ORDERED



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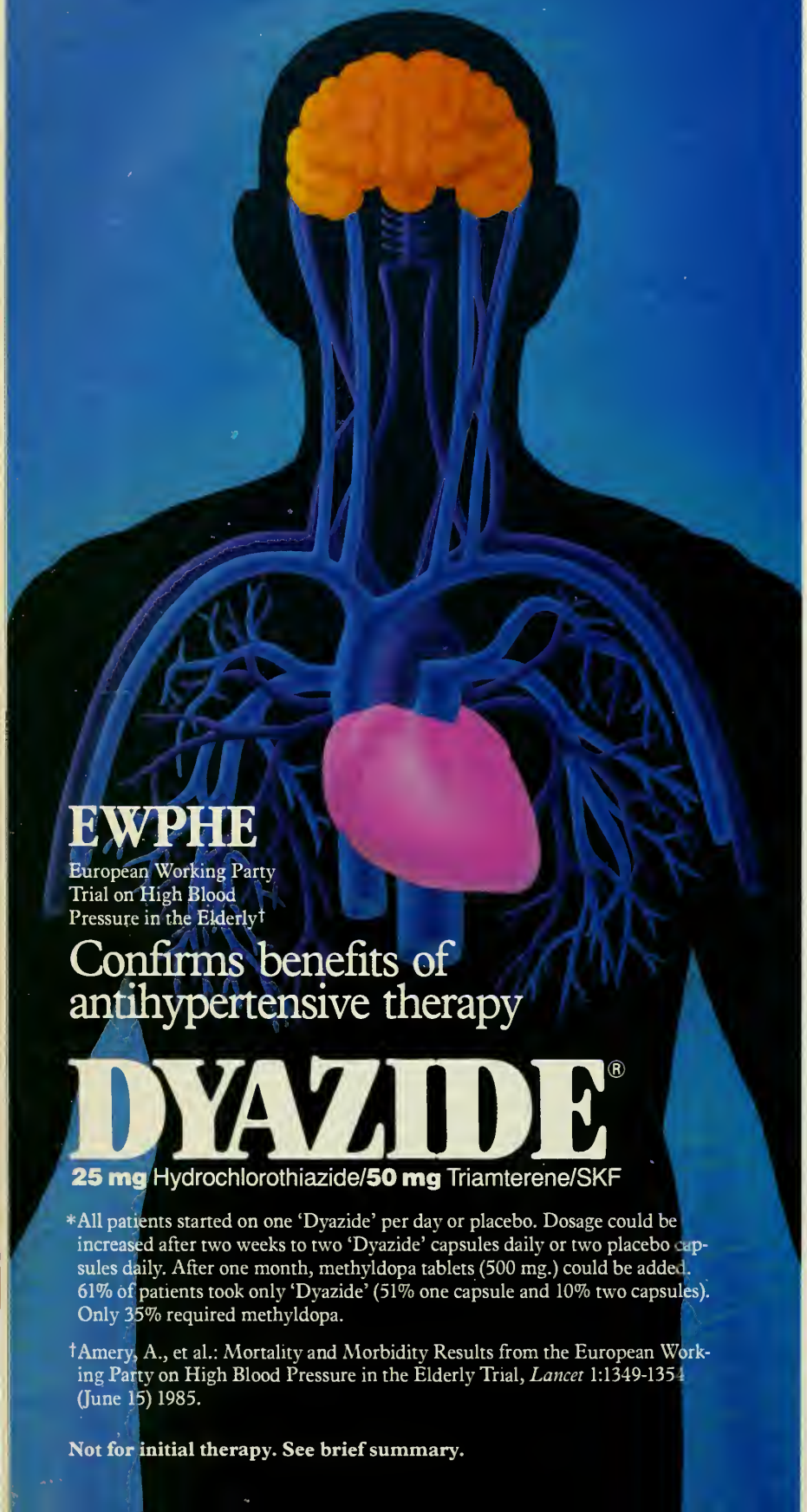

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25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

*All patients started on one 'Dyazide' per day or placebo. Dosage could be increased after two weeks to two 'Dyazide' capsules daily or two placebo capsules daily. After one month, methyldopa tablets (500 mg.) could be added. 61% of patients took only 'Dyazide' (51% one capsule and 10% two capsules). Only 35% required methyldopa.

†Amery, A., et al.: Mortality and Morbidity Results from the European Working Party on High Blood Pressure in the Elderly Trial, *Lancet* 1:1349-1354 (June 15) 1985.

Not for initial therapy. See brief summary.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do **not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Marshall B. Block, M.D.
Editor

ARIZONA MEDICINE

JOURNAL OF ARIZONA MEDICAL ASSOCIATION

JANUARY 1987, VOL. XLIV, NO. 1

The PRO: Should We Be Involved?

By having been involved with peer review activities over the last five years, I have had an opportunity to understand the mechanism of the review process and gain a better feeling for what is transpiring in the medical community throughout our state. By and large, physicians in this state are practicing good to excellent medical care. There are differences in philosophy at times between how one would approach a problem from a medical point of view, but overall, the things that are being done to patients seem appropriate, and for the most part, the results are comparable to elsewhere in the United States if not, on occasion, better. This raises several questions which need to be addressed. Why do we need the PRO? Is it doing anything worthwhile? Will participation by physicians be more detrimental than helpful in the long run?

All three questions are difficult to answer, and perhaps were brought home by a recent conversation I had with a colleague. He verbally accosted me and berated my involvement in the state peer review organization, for he felt we were being tools of the federal government and were justifying and legitimizing the Medicare program. He felt that we should disengage ourselves from the PRO in order to allow the system to fall on its face. A key fallacy with this point of view is that the federal government will continue to insist on a monitoring system to ensure that its funds are being utilized in a fashion that is to the benefit of the beneficiaries, i.e., our patients. There is strong public support for a watchdog organization. There is also very strong sentiment within and without the government that no one can do this as effectively as physicians. Bureaucrats, administrative assistants, and even nurses, can sometimes not understand the intricacies of medical decisions, and can come to very misleading interpretations of data without the seasoned knowledge of a practitioner interfacing with the pure statistical information which is generated from our computer systems. Thus, some sort of monitoring procedure will always be needed, wanted, and demanded, no matter what form ultimately Medicare reimbursement takes. The review organization in this state (Health Services Advisory Group) is being run by practitioners who are concerned and responsible physicians. The physicians who review are interested in making certain that what is being done is appropriate, and that if it is not, proper corrective actions are taken without unduly sacrificing the practitioners or hospitals in question. We spend long hours, late at night, agonizing over many decisions and try placing ourselves in the situations we review. Those of us who are involved in the review process feel that it should remain in our hands rather than elsewhere, in order to ensure that the interpretation of the information which is generated is interpreted correctly. This, then, is the major reason for our continued involvement.

Have we accomplished anything? This is another difficult question to answer. At the conclusion of our fist two-year contract as the PRO for the state of Arizona, we uncovered several instances of divergent behavior amongst practitioners and hospitals. However, the number of such aberrations are infinitesimally small compared to the total number of cases that we have reviewed. We therefore do

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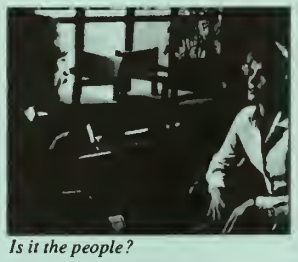
not and cannot claim to have uncovered a great deal of "dirty laundry" during this time, which is a tribute to the caliber of medicine being practiced in our state. We, however, may have had significant impact by our mere presence. By establishing certain criteria for admission and now discharge, by mandating certain procedures being performed on an outpatinet basis rather than inpatient, we may have altered practice behavior in a cost-effective fashion, and thus may have had a tremendous impact on the cost of medical care in our state. However, there has now been a dramatic shift from the inpatient to the outpatient environment in delivery of health care during the last five years. With this shift has been a greater expenditure of funds for outpatient care, which in turn is now leading to the movement for outpatient review and control. Furthermore, with the growth of prepaid plans such as federally-approved HMOs, the PRO will be looking at their outpatient and inpatient practices for the first time. We will thus be in a position to compare fee-for-service versus prepaid health care delivery from a quantity as well as a quality point of view. The overall impact of the PRO on health care delivery in our state will, I believe, dramatically increase in the future. There will probably be those who will not be pleased with this assessment, but I think if we are practicing good medicine, we all have nothing to be concerned about. The continued presence of physicians in peer review organizations and in peer review activities may help to reveal things which will improve both ours and the public's perception of medical care delivery in our state. As a former president of the American Medical Association recently stated at an Arizona Medical Association Board of Directors' Meeting, physicians *must* stay involved in the review process even though it may create conflicts with their colleagues.

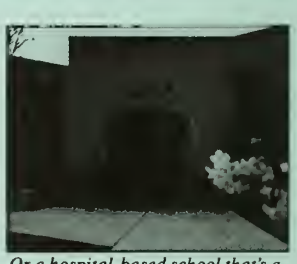
Those of us involved in the PRO review process welcome constructive input from our colleagues and urge them to participate with us in this necessary activity. ■

Marshall B. Block, M.D.

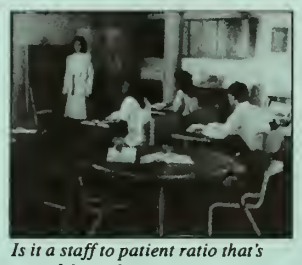
What makes Palo Verde one of the Nation's finest psychiatric hospitals?



Is it the people?



Or a hospital-based school that's a national model?



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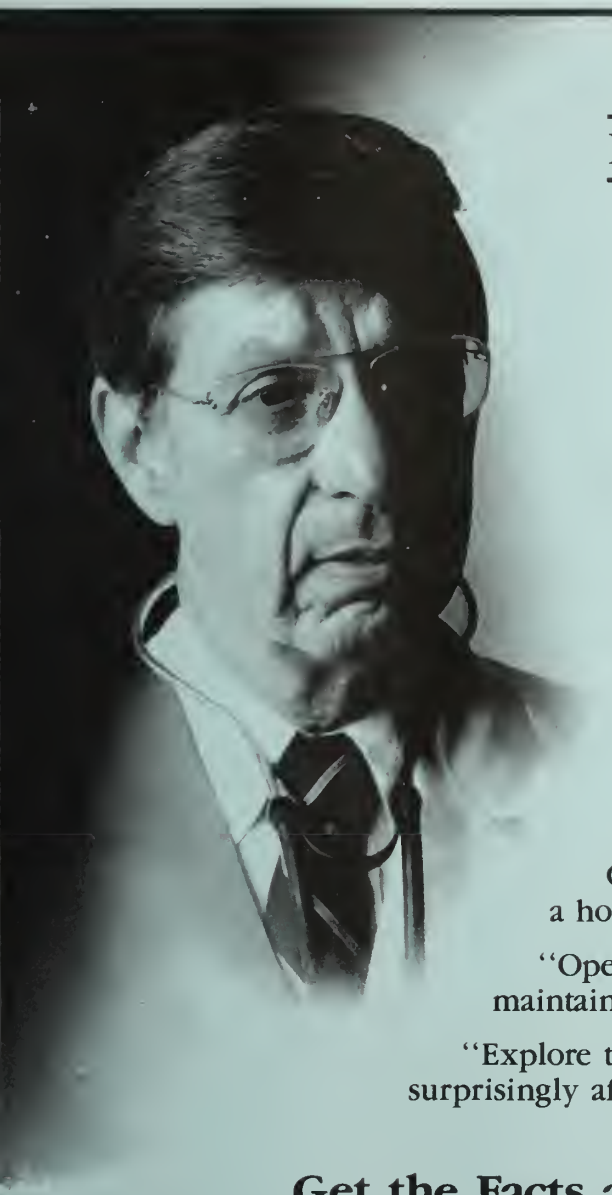

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Physicians in the News

Lisa Wilkinson-Fannin, M.D., was welcomed recently to the 14-member St. Joseph's Hospital and Medical Center Board of Directors. Dr. Wilkinson-Fannin began her two-year term as one of two physicians on the board.

"It's particularly important to have physicians on the board when health care costs figure so heavily into decisions that are made," she said. "Doctors are aware of patient care needs and can help the decisionmakers prioritize those needs."

A native of England, Dr. Wilkinson-Fannin has served as chairwoman of the Division of Neuroanesthesiology at the Barrow Neurological Institute (BNI) at St. Joseph's since 1974. She also began a two-year rotation as chairwoman of the St. Joseph's anesthesiology division in January.

Before joining the BNI, Wilkinson-Fannin was an assistant professor at McGill University and on staff at Montreal Neurological Hospital in Canada. She received her medical degree at London University and was a fellow of the Faculty of Anaesthesia of the Royal College of Surgeons of England.

Dr. Wilkinson-Fannin serves on the legislative committee of the Arizona Medical Association and is president of the Maricopa County Society of Anesthesiologists. She is married to attorney and lobbyist Robert Fannin, the son of former Senator Paul Fannin.

Franklin D. Loffer, M.D., Phoenix, has completed his term as 1986 president of The American Association of Gynecologic Laparoscopists (AAGL) which has concluded its 15th Annual Meeting at the Hyatt Regency Grand Cypress Hotel.

John L. Marlow, M.D., of Washington, D.C. succeeds Dr. Loffer as President.

Dr. Loffer will continue in active participation with the organization. He is also the program chairman of the 3rd World Congress on Hysteroscopy which will be held in Miami in January, 1987

Dr. Loffer received both his A.B. and M.D. degrees from Stanford University. He is currently in private practice in Phoenix. Among his hospital staff appointments are Good Samaritan Hospital, John C. Lincoln Hospital, Memorial Hospital, Phoenix Baptist Hospital, and St. Luke's Hospital, all located in Phoenix, and Scottsdate Memorial Hospital.

Dr. Loffer serves on the Blue Cross/Blue Shield Board of Directors and as a member of the Professional Committee, Planned Parenthood of Central and Northern Arizona.

Dr. Loffer is married to the former Patricia Sparger. They are the parents of two children, Kimberly and Franklin. The family resides in Scottsdale.

Dr. Loffer is a member of the Board of Directors, Arizona Medical Association; an Alternate Delegate, American Medical Association; and a member of the Maricopa County Medical Society.

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Computers in Medical Research and Practice

Computers are powerful *tools*, intended to facilitate functions previously performed in less efficient and less flexible fashion. In the realm of research, they can assist the investigator in planning, designing, implementing and analyzing projects. At the University of Arizona College of Medicine, a variety of research projects have used computer facilitation. These include the large-scale Specialized Center for Research (SCOR) epidemiologic study, which has been extant for 15 years now. Computer data are entered on a large cohort of adults and children in various sub-projects within the SCOR study. Detailed, sophisticated statistical and epidemiologic analyses are conducted to sort out various risk factors for chronic obstructive lung disease, for identifying predictive factors from the newborn period forward for airways disorders later in life, and similar questions.

A large variety of investigators employ statistical analyses of their data in collaboration with the Biostatistics Office. An additional cohort use computer assistance in analyzing research data in the educational environment, employing optical scanners to read directly from forms into the computer data bank, sophisticated analytic programs, and ultimately, using computer-based instruction as the data-input for research into such aspects of learning as clinical problem-solving abilities of students and residents.

Practice applications of computers include everything from assistance with management of detailed billing systems, through computerized patient and laboratory records, to continuing medical education. Many offices in our community, the practice plan of the full-time faculty, and the University Medical Center use available or self-designed programs to do all patient-related accounting. The University Medical Center, in cooperation with the College of Medicine, has developed an ambulatory patient record system, using the CoStar System. Family practice, pediatric cardiology and selected units record their patient encounters in computer format, which is then entered into the data bank, providing the physician with updated records each time the patient is seen. Incorporated into this system are reminders to the physician of important points in the ongoing management of patients, such as clues to lifestyle practices, immunization status and a variety of time-related screening procedures.

The Clinical Pathology section of the Department of Pathology has on-line laboratory reporting for almost all values, including microbiologic data. Physicians can access the information for their patients by using an assigned password, and receive instantaneous reports, in printed form, of all completed laboratory procedures, and a progress report on those that are pending.

Intensive Care Units rely heavily on computerized data displays on patients with critical illnesses. Programs keep track of vital data, show trend analyses and can be programmed to predict events and to indicate desired clinical options.

Continuing medical education programs, designed for individual use, can assist practitioners in remaining current in specific areas. This development is in its infancy, but is rapidly growing, with significant instructional programs in many general medical and specialty areas. Faculty at the College are actively developing software which employ CME principles, for use by the practitioner.

This sampling of computers in research and practice is just that . . . a sampler. The full scope of activities would require a full article, just to catalogue the multiple uses of computers in these areas. If educational uses were added to the list, then several articles would be necessary to encompass all that is being done. We have entered the computer era, and progress is swift and exciting, offering multiple opportunities to use this new tool to make medical research and care more efficient and more exact. The College is moving with the tide of development, and in many areas, leading the way. ■

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Clinical Investigation

Increased Vertebral Bone Mineral in Response to Reduced Exercise in Amenorrheic Runners

JILL S. LINDBERG, MD, *Fort Sam Houston, Texas;* MALCOLM R. POWELL, MD; MARJORIE M. HUNT; DIANE E. DUCEY, *and* CHARLES E. WADE, PhD, *San Francisco*

Seven female runners found to have exercise-induced amenorrhea and decreased bone mineral were reevaluated after 15 months. During the 15-month period, four runners took supplemental calcium and reduced their weekly running distance by 43%, resulting in an average 5% increase in body weight, increased estradiol levels and eumenorrhea. Bone mineral content increased from 1.003 ± 0.097 to 1.070 ± 0.089 grams per cm.^{2} Three runners continued to have amenorrhea, with no change in running distance or body weight. Estradiol levels remained abnormally low and there was no significant change in the bone mineral content, although all three took supplemental calcium. We found that early osteopenia associated with exercise-induced menstrual dysfunction improved when runners reduced their running distance, gained weight and became eumenorrheic.

(Lindberg JS, Powell MR, Hunt, MM, et al: Increased vertebral bone mineral in response to reduced exercise in amenorrheic runners. West J Med 1987 Jan; 146:39-42)

Exercise-induced amenorrhea has recently received much attention following reports that bone mineral content in the young women with this disorder is reduced to levels seen in postmenopausal women with osteoporosis.[1-3] Suggested causes of exercise-induced osteopenia include distance running, reduced body fat, decreased estradiol levels and increased prolactin levels.[2-6] In a recent study, we postulated that reducing running distance and increasing calcium intake would improve bone density in amenorrheic runners.[1] After 15 months, we reevaluated 7 of the 11 amenorrheic runners in our original study. We present the results of our follow-up.

Subjects and Methods

Seven of the eleven original runners identified as having secondary amenorrhea with osteopenia were available for reevaluation after 15 months. Only seven of the eleven original runners could be found and would agree to restudy. The eleven originally studied were runners who volunteered on the basis that they were running at least 20 miles per week and had amenorrhea for at least one year. Reevaluation consisted of repeat vertebral bone mineral analysis, weight measurements and measurement of estradiol levels. The patients were interviewed twice, at 15 months and at 17 months, regarding changes in calcium intake, weekly running distance and gynecologic history to verify their information.

Random plasma estradiol levels from each runner were measured in frozen specimens obtained on initial evaluation during amenorrhea and at 15 months' follow-up either during continuous amenorrhea or during the normal cycle. An estradiol level was determined by a radioimmunoassay (Diagnostic Products, Los Angeles) with a sensitivity of 7 pg per ml and a within-assay coefficient of variability of 10%. Spinal bone mineral measurements were made using a dual photon absorptiometer (Model DP 3, Lunar Radiation Corporation, Madison, Wis) and a gadolinium 153 radiation source with a better than 2% short-term measurement precision (reproducibility). Short-term precision has been measured on the same instrument used for this study as between 1.3% and 1.9% in three persons with normal, low normal and reduced spine mineral content. High-precision measurement is accomplished by carefully positioning subjects, remeasuring the same lumbar segments, using a computer-based edge finder

From the Departments of Medicine (Dr Lindberg) and Clinical Investigation (Ms Hunt and Dr Wade), Letterman Army Medical Center; the Nuclear Medicine Consultants and the Department of Medicine, University of California, San Francisco, School of Medicine (Dr Powell); the Department of Physical Therapy, Ralph K. Davies Medical Center (Ms Ducey), and the Division of Combat Casualty Care, Letterman Army Institute of Research (Dr Wade), San Francisco. Dr Lindberg is now with the Division of Nephrology, Department of Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

This study was presented in poster format at the 67th Annual Meeting of the Endocrine Society held in Baltimore from June 19 to 21, 1985.

Reprint requests to Jill S. Lindberg, MD, Div of Nephrology, Dept of Medicine, Brooke Army Medical Center, Ft Sam Houston, TX 78234.

for automatic determination of bone edges and by measuring several segments, the first through the fourth lumbar segments in this instance. Our precision data are supported by published reports on the method using a variety of instruments.[7-9]

Subject 1

This 33-year-old woman had amenorrhea for ten years, five years after beginning a program of running 160 km per week. On reevaluation, she has been eumenorrheic for six months, starting two months after decreasing her running distance by 48 km per week. She had a 4.5-kg weight gain and a 6.5% increase in vertebral bone mineral (Figure 1).

Subject 2

This 31-year-old woman had amenorrhea for 3 years, 1½ years after beginning a program of running 32 km per week and aerobic dancing four times per week. On reevaluation, she has been eumenorrheic for four months after discontinuing her running program but continuing aerobic dancing. During this period, she has had no stress fractures, compared with two per year previously. She has had a 3-kg weight gain and an 11% increase in vertebral bone mineral content.

Subject 3

This 26-year-old woman had amenorrhea for three years after beginning a program of running 64 km per week, swimming 8 km per week and cycling 67 km per week. On reevaluation, she has been eumenorrheic for six months, beginning two months after discontinuing her running but continuing her swimming and cycling. She has had no stress fractures, compared with two per year previously. She has had a 2-kg weight gain and a 5.5% increase in vertebral bone mineral content.

Subject 4

This 32-year-old woman had amenorrhea for eight years after beginning a program of running 72 km per week. On reevaluation, she has been eumenorrheic for six months, starting five months after she decreased her running distance by 24 km per week. She has had no stress fractures, compared with two per year previously. She has had a 1.5-kg weight gain and a 3.3% increase in vertebral bone mineral content.

Subject 5

This 38-year-old woman has had amenorrhea for four years, two years after starting a program of running 40 km per week. On reevaluation, she has continued the same exercise program and continues to have amenorrhea. A repeat measurement of her vertebral bone mineral content shows a 2% increase, and her weight has further decreased by 0.3 kg.

Subject 6

This 28-year-old woman had oligomenorrhea for 8 years and amenorrhea for 1½ years, 1 year after beginning a program of running 72 km per week and sustaining a 5-kg weight loss. She has no change in body weight, and she continues to have amenorrhea. A repeat vertebral bone mineral measurement showed a 2.3% decrease.

Subject 7

This 32-year-old woman has had amenorrhea for four years, two years after beginning a program of running 38 km per week. On reevaluation, she continues to run 38 km per week. Her weight has further decreased by 3 kg, and she continues to have amenorrhea. A repeat vertebral bone mineral determination showed a 3.5% decrease.

Results

All seven runners are white women who, on initial evaluation 15 months previously, had amenorrhea and were found by vertebral bone mineral analysis to have L-1 to L-4 bone mineral content below the normal range. During the interim period, all seven runners remained physically active and all were taking calcium supplementation (Table 1). The four runners (subjects 1 to 4) who reduced their weekly running distance increased their body weight by at least 3%, became eumenorrheic, had increased estradiol levels to within the normal range (45 to 400 pg per ml) and showed increased bone mineral content, changing as a group from 1.003 ± 0.097 to 1.070 ± 0.089 grams per cm^2 ($\bar{X} \pm$ standard deviation). In these four runners, the frequency of stress fractures was reduced. The three runners (5 to 7) who did not reduce their weekly running distance had no increase in body weight, continued to have amenorrhea with abnormally low estradiol levels and showed no significant improvement in bone mineral content.

The overall change in bone mineral in both groups, as determined by vertebral bone mineral analysis, was positively correlated with the change in body weight ($N = 7$, $r = +0.88$, $P < .005$) (Figure 2). The increase in bone density in the runners who reduced their running distances was significantly greater by t test ($P < .02$) compared with the runners who did not reduce exercise.

Exercise has been believed to be important in preventing bone mineral loss.[10,11] The total body calcium level is re-

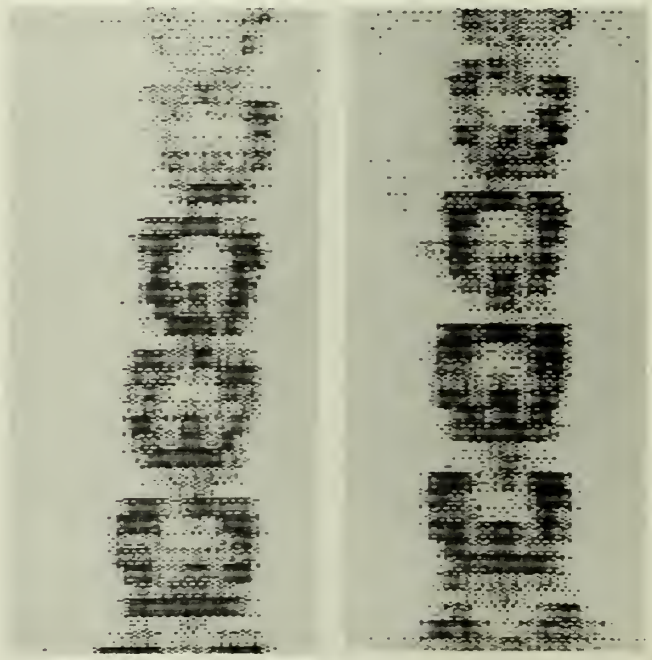

Figure 1.—Transmission gadolinium 153 scans of subject 1, before (on the left) and 15 months after (on the right) exercise modification showing a 6.5% increase in bone density in the lumbar spine. (These transmission scans were printed at the same time from the original data sets and then were photographed on the same negative for optimum comparability.)

TABLE 1.—*Changes in Female Runners During a 15-Month Follow-up*

Subject	Current Menstrual Status*	Height, cm	Weight, kg, Pre/Post	Bone Density, grams/cm², Pre/Post	Weekly Distance Run, km Pre/Post	Other Sports Pre/Post	Estradiol Level, pg/ml Pre/Post†	Calcium Supplement, mg/day
1	E	167.0	60.0/64.5	1.084/1.155	160/112	0/0	17/50	750
2	E	170.2	54.0/57.0	0.879/0.975	32/0	Aerobics/Aerobics	18/349	1,500
3	E	174.0	60.0/62.0	1.076/1.135	64/0	Swim/Swim Cycling/Cycling	48/67	500
4	E	152.4	45.5/47.0	0.976/1.014	72/48	0/0	UD/80	350
5	A	165.1	47.3/47.0	0.900/0.925	40/40	0/0	UD/UD	1,500
6	A	162.6	51.0/51.0	0.915/0.894	72/72	0/0	10/42	900
7	A	165.1	53.0/50.0	0.868/0.838	38/38	0/0	45/9	1,500

*E=eumenorrheic, A=amenorrheic.
†UD=undetectable, less than 7 pg/ml.

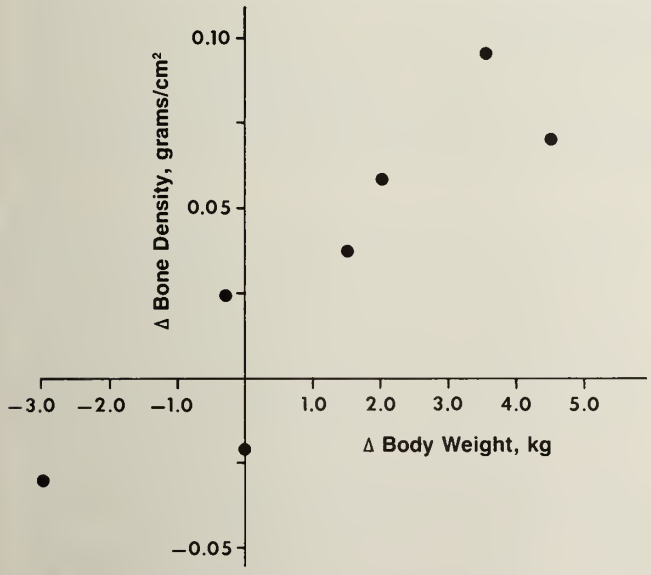

Figure 2.—Relationship of change in body weight to change in bone density over a 15-month period in 7 women with a diagnosis of osteopenia due to exercise-induced amenorrhea.

ported to be 11% higher in male marathon runners than in nonrunners.[12] Physically active women have been noted to have bone mineral values higher than sedentary controls as determined by cortical bone measurements in the radius.[13] Recent work, however, suggests that runners with amenorrhea may show a mineral loss in trabecular bone in the absence of a significant change in cortical bone mineral levels.[1,2]

A variety of factors are suggested to be involved in the loss of bone mineral with exercise-induced amenorrhea. Cann and Genant found spinal trabecular mass determined by quantitative computed tomography to be reduced by 25% to 30% in physically active, amenorrheic women and postulated that this condition was caused by the low plasma estradiol levels observed in ten patients.[3] Linnell and co-workers in their study of ten amenorrheic runners found reduced body fat to be the most important factor in reducing bone mineral.[4] Drinkwater and associates found the distance run and low estradiol levels to be the significant factors associated with decreased bone mineral content in runners with amenorrhea.[2] Dietary factors, specifically a calcium intake of less than 1,000 mg per day, may also contribute to the development of osteopenia in these athletes.[14]

Though the suggested causes of reduced bone mineral content appear interrelated, a single factor has yet to be identified. In light of these findings, we advised the amenorrheic runners in the present study to take calcium supplementation of 1,500 mg per day and to reduce their weekly running distance by 16 to 32 km. Similar recommendations have since been proposed by Marcus and colleagues[15] and supported by Heath.[16]

Fifteen months later, four runners had reduced their running distance, yet remained physically active. These runners took 350 to 1,500 mg of calcium supplement per day. When they were reevaluated, their bone density had increased by 6.6% (range 3.3% to 11.0%), an average increase of more than three times the precision of the measurement.

The alterations in bone density in the present study correlate with the changes in body weight. The runners whose body weights increased by more than 3% also had increased bone densities. The relationship between these two variables is not clear, but both may be associated with changes in running distance or menstrual function. Though not conclusive as to the cause of decreased bone mineral, our findings show that an increase in body weight in amenorrheic runners with osteopenia correlated with an increase in mineral content.

Many healthy-appearing female athletes present to physicians with histories of long periods of amenorrhea. In the past, this amenorrhea has been thought to be benign, its main complication being infertility. It is now apparent that the consequences of long-term exercise-induced amenorrhea may also include early osteopenia and an increased frequency of stress fractures. We found that our patients who decreased their running distance subsequently increased body weight, reestablished a normal menstrual cycle, reduced the frequency of stress fractures and had increased bone mineral content.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Hospital Admission Following Rigid Esophagoscopy

QUESTIONS:

When should rigid esophagoscopy be used?

When is it medically necessary for patients who undergo rigid esophagoscopy to remain in hospital overnight?

If it is not necessary for all such patients to stay in hospital overnight, are there criteria that would identify patients who should receive this level of observation?

OPINION:

In the opinion of the Scientific Advisory Panel on Otolaryngology/Head and Neck Surgery, rigid esophagoscopy is considered established practice for the diagnosis of esophageal neoplasms, strictures and burns as well as inflammatory, metabolic, congenital, traumatic and neoplastic diseases. It is preferred by clinicians for the removal of foreign bodies, dilatation of esophageal strictures and retrieval of biopsy specimens from esophageal lesions. Rigid esophagoscopy is also standard practice for the evaluation of patients with cancer in the upper respiratory tract.

Hospital admission to observe a patient overnight following this procedure should be determined by the endoscopist based on the patient's physical condition and the likelihood of postoperative complications. Among the indications that support the medical necessity of hospital admission are the following: actual or suspected perforation of the esophagus, any unexplained tachycardia, fever, throat or chest pain, the presence of air in the soft tissues of the neck or mediastinum, evidence of general medical instability and when there is no responsible person to assist the patient should it be necessary to return to the hospital. Because the risk of perforating a patient's esophagus is high in first-time dilatation of strictures, after the removal of any foreign body and with any deep biopsy or manipulation of an esophageal tumor, it is established practice to admit these patients to hospital for 24 hours observation. For some patients who have had an uncomplicated diagnostic esophagoscopy that showed no lesions, caused no bleeding, collected no biopsy specimens or involved no other uses of the instrument, some physicians feel it is reasonable to discharge them the day of the procedure following several hours of observation.

Iodine Absorption After Topical Administration

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Absorption from povidone-iodine preparations after topical administration has been reported to be negligible, but an elderly woman had increased serum iodine levels with possible metabolic complications after povidone-iodine solution was applied to decubitus ulcers.

(Dela Cruz F, Brown DH, Leikin JB, et al: Iodine absorption after topical administration. West J Med 1987 Jan; 146:43-45)

Iodine is a topical germicidal agent effective against a wide spectrum of organisms including bacteria, viruses, fungi and protozoa.[1] Iodine is available as solutions and alcoholic tinctures and as iodine compounds such as iodophors. Iodophors were developed following early reports of skin irritation, severe hypersensitivity reactions and systemic absorption of iodine from iodine tinctures.[2,3] Iodophors are compounds of iodine linked to surfactants that act as carriers or solubilizing agents for iodine. A small amount of free iodine is released in solution, thereby minimizing toxicity while preserving moderate germicidal activity of the element.[1]

One of the most extensively used iodophors is the complex of polyvinylpyrrolidone (povidone) and iodine. Initial studies of this agent in animals indicated negligible systemic absorption of iodine following topical administration.[4] Since then there have been a number of reports of possible iodine toxicity occurring after topical administration of the product in humans.

Most cases have involved the application of povidone-iodine to burn wounds involving extensive areas of the body surface. In this report we describe a case of increased serum iodine levels associated with metabolic abnormalities after topical povidone-iodine treatment in a patient with decubitus ulcers involving a relatively small body surface area. We also present a review of topical iodine absorption and systemic complications associated with topical administration.

Report of a Case

The patient, an 83-year-old woman, had a history of hypertension, congestive heart failure, type II diabetes mellitus and asthma. Early in February 1985 she sustained a left parietal lobe infarct resulting in right hemiparesis. After stabilization, the patient was transferred to a rehabilitation institute. Five weeks after the stroke, however, she was readmitted to her local hospital for treatment of decubitus ulcers located on the anterior surface below each knee. The patient was subsequently transferred to Cook County Hospital (Chicago) a week later.

Upon transfer the patient was noted to be afebrile and somewhat lethargic. Remarkable findings on physical examination included an expressive aphasia along with right-sided motor weakness and bilateral ankle clonus. Two decubitus ulcers were observed approximately 5 cm below each patella. The right ulcer was 10 by 10 cm and the left was 6 by 6 cm. The ulcers were granulating well without any foul odor or discharge. They were estimated to comprise 2% to 3% of her total body surface area.

The patient had been receiving gauze soaked with 10% povidone-iodine solution (1% free iodine, Pharmadine, Sherwood) packed into her wounds every four hours over the preceding three to five weeks. Other medications the patient had been receiving were digoxin, methyldopa, a sustained-release theophylline preparation, nitroglycerin patches (Nitro-Dur, Key) and subcutaneous injections of heparin. No iodine dye study had been done over the previous month.

During the succeeding week, a number of complications developed, including persistent diarrhea, an upper gastrointestinal tract hemorrhage due to erosive gastritis and bronchospasm due to congestive heart failure. During this time the patient also had increasing renal insufficiency, primarily manifested by a rise in the serum creatinine level from 1.8 to 3.5 mg per dl, along with a metabolic acidosis: pH 7.34, serum bicarbonate decreasing from 19.8 to 10.8 mEq per liter and a corresponding anion gap of 18. A lactate level was 46.9 mg per dl. Her serum chloride concentration peaked at 127 mEq per liter and serum sodium at 156 mEq per liter. The calculated serum osmolarity increased to 340 mosm per liter.

Because of these findings, a serum iodine level was measured and found to be 2,700 μg per dl (normal 4 to 9). Povi-

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done-iodine dressings were discontinued, and over the next ten days the patient's serum creatinine level declined and stabilized at 2.9 mg per dl. Her acidosis and anion gap resolved. The serum chloride level decreased to 89 mEq per liter, the serum sodium to 126 mEq per liter and serum osmolarity to 286 mosm per liter. A repeat serum iodine concentration 15 days later showed that the serum iodine level had declined to 21 μg per dl. Thyroid function test results remained within normal limits.

The patient died six weeks following transfer due to multiple complications including sepsis, congestive heart failure and respiratory failure. Necropsy was not done.

Comments

Iodine Absorption

Povidone-iodine is available in a number of different formulations including solutions, ointments, foams, surgical scrubs and vaginal preparations. The available iodine content in the preparations varies from 0.2% in the ointment to 1% in the solution and vaginal preparations.[5]

The reports of iodine absorption from topical povidone-iodine solution suggest that absorption is enhanced when the compound is applied to denuded skin, mucosal surfaces with high absorptive capacity or extensive areas of intact skin. The evidence for iodine absorption includes documented serum iodine concentrations and thyroid function abnormalities.

Most cases in which increased serum iodine concentrations are reported have involved burn patients.[6-8] In addition, serum iodine concentrations have become elevated following application of povidone-iodine dressings to extensive surgical wounds,[9,10] after vaginal instillation[11] and after application to the umbilical cord and an inch of surrounding skin of neonates.[10] Perinatal exposure to povidone-iodine infusion resulted in elevated iodide levels in both mothers and neonates.[12] Absorption of iodine after povidone-iodine was applied to a decubitus ulcer has been reported in one other case involving a patient with an extensive sacral decubitus ulcer (about 13 by 11 cm).[9] In addition, increased postoperative protein-bound iodine concentrations have resulted from preoperative skin preparation and vaginal douches.[13]

Povidone-iodine applications to surgical wounds of neonates[14] and povidone-iodine baths used to cleanse the entire body surface of young children[15] have resulted in abnormal thyroid function test findings (elevated thyroid-stimulating hormone and normal thyroxine and triiodothyronine levels). Long-term treatment of a perineal fistula with a povidone-iodine scrub and iodoform-impregnated packing has caused clinical signs and symptoms of hypothyroidism.[16]

The absorption and elimination of iodine following topical administration have not been well documented. The extent of absorption appears to be related to the size of the area of application and may possibly be related to the povidone-iodine vehicle.

In their review of burn patients, Hunt and co-workers found that the extent of iodine absorption was directly related to the size of the area of application.[6] Serum iodine concentrations ranged from 595 to 1,440 μg per dl (normal 0 to 3) after application of povidone-iodine ointment to burns of 0% to 15% total body surface area (TBSA); in patients with 15% to 30% TBSA burns, from 910 to 2,390 μg per dl, and in those with burns greater than 30% TBSA, from 1,200 to 4,900 μg per dl. The amount of iodine absorbed may also be directly related to the amount of partial thickness burn.[7,8]

The absorption of iodine has not been associated with a particular formulation of povidone-iodine. The occlusive nature, however, of povidone-iodine ointment would be expected to enhance iodine absorption through intact skin as compared with the solution. Conversely, applying povidone-iodine solution to wounds would be expected to result in greater absorption than applying the ointment because of better diffusion of dissolved iodide to the dermal surface.

At present, the form of iodine absorbed—whether it is povidone-iodine, free iodine or iodide—is unknown.[7] The toxic moiety of iodine is also undetermined. Povidone has been detected in serum by mass spectrometry, evidence that at least partial absorption of povidone occurs.[8] The site of reduction of iodine to iodide is also unknown.[7]

Iodine is excreted primarily by the kidneys, and the renal clearance of iodine is directly related to the glomerular filtration rate.[6,9] Renal function and the duration of povidone-iodine administration would be expected to influence systemic iodine accumulation.

Renal insufficiency results in higher and more prolonged elevations in serum iodine concentrations, although the rate of decline of serum iodine concentrations over time has not been well characterized in patients with either normal or decreased renal function. In our patient, the second serum iodine concentration was still elevated, although greatly decreased from the first measurement, 15 days after the povidone-iodine treatment was discontinued. Urinary iodine excretion in patients with renal failure has been shown to be minimal—that is 150 μg per day—compared with that in patients with normal renal function—912,000 μg per day.[6] Immature kidney function may explain iodine accumulation in neonates.

Even patients with normal renal function show relatively rapid elevations of serum iodine. Hunt and colleagues observed that in patients with normal renal function and greater than 30% TBSA burns, peak serum iodine concentrations ranged from 7,600 to 32,000 μg per dl after five days of topical therapy.[6] Serum iodine concentrations continued to increase until treatment was discontinued and remained high for as long as seven days after the povidone-iodine treatment was discontinued.

There are no data correlating either frequency or duration of povidone-iodine administration with serum iodine concentrations, but longer treatment is expected to potentiate iodine accumulation. In our patient, prolonged application of povidone-iodine dressings to a relatively small surface area may have enhanced iodine accumulation.

Clinical Manifestations of Iodine Absorption

A constellation of metabolic and electrolyte abnormalities has been reported to occur with elevated serum iodine concentrations, including metabolic acidosis,[6-9,17,18] hyperchloremia,[9,17,18] hypernatremia,[6,17,18] hyperosmolarity[17] and renal failure.[7-9,17,18] All of these systemic complications were observed in our patient.

The cause for metabolic acidosis is unclear. It has been postulated to be due to the acidic pH (2.43) of povidone-iodine or to the consumption of bicarbonate by the combination of free iodine with serum sodium bicarbonate, illustrated by the following equation: $6NaHCO_3 + 3I_2 \rightarrow 5NaI + NaIO_3 +$

$6CO_2 + 3H_2O$.[19] The equation is driven to the right by respiratory elimination of carbon dioxide. Determination of a specific cause of metabolic acidosis in previously reported cases has been complicated by concurrent disorders such as sepsis, shock, renal failure, ketoacidosis and lactic acidosis.[8] In one report, these potential causes were not temporally related to the metabolic acidosis.[17] In still other reports, serum lactate levels were normal.[8,9] The metabolic acidosis occurring in our patient may have been partly caused by persistent diarrhea.

Hyperchloremia probably represents spurious elevations in the serum chloride due to interference of the assay by iodine.[9] Serum chloride determinations made by the Technicon STAT/ION autoanalyzers result in false elevations in serum chloride levels in a nonlinear fashion. Thus, serum chloride concentrations may be falsely high even at low iodide levels when this method is used.[20] In the presence of elevated iodine concentrations, the silver halide precipitation assay should be used for an accurate measurement of serum chloride concentration.

Hypernatremia has been reported in burn patients treated with topical povidone-iodine,[6,17,18] but Hunt and associates observed metabolic acidosis and serum sodium concentrations greater than 150 mEq per liter in only three burn patients with renal failure. Serum electrolytes remained within normal limits in all patients with normal renal function, even with increased iodine concentrations. Although the hypernatremia could be attributed to excessive insensible and respiratory water loss, exogenous sodium administration, renal dysfunction and sepsis, it has been reported to occur shortly after starting povidone-iodine treatment and to resolve within 24 hours of discontinuation in two other cases.[17,18]

Elevations in the serum osmolarity may result from the osmotic effects of free iodine in the blood.[6] It may also be caused by hypernatremia or perhaps by povidone, although the latter is unproved.

Nephrotoxicity due to iodine has not been confirmed by pathologic examination in humans.[8] The possibility of drug-induced nephropathy due to drugs such as aminoglycosides or cephalothin or renal dysfunction due to sepsis and volume contraction cannot be excluded in some cases. The nephrotoxic potential of povidone is unknown.[7]

Clinical hypothyroidism[16,21] and hyperthyroidism[22] have been associated with topical povidone-iodine therapy, as have laboratory abnormalities consistent with depressed thyroid function.[12,15,23] There was no evidence of thyroid dysfunction in our patient.

Other symptoms attributed to iodine toxicity in the literature include elevated serum aminotransferase levels,[7] hyperbilirubinemia,[8] changes in sensorium (agitation, confusion, hallucinations),[7,24] neutropenia[24] and hypoxemia.[24] Topical povidone-iodine therapy has also been implicated as a possible cause of severe stomatitis and diarrhea in a burn patient.[24] Again, in each case, the patient course was complicated by other potential causes of symptoms, such as infection, sepsis and cardiopulmonary arrest. Death has not been directly attributed to topical iodine toxicity up to this time.

In summary, high iodine concentrations imply toxicity. Clinical evidence of cell or organ toxicity, however, is as yet undetermined. There are no clinical correlations with serum iodine determinations, and the actual concentration at which toxic symptoms may occur is unknown. Metabolic abnormalities have been reported to occur concurrently with elevated serum iodine concentrations, but increased iodine concentrations have also occurred without any clinical or laboratory manifestations of possible toxicity.[6,7] Thus, there does not appear to be a characteristic syndrome of iodine intoxication following topical administration. It is possible that a certain patient population may be at greater risk, such as patients with renal dysfunction.

We believe that the metabolic acidosis, hypernatremia and renal insufficiency observed in our patient were partly due to iodine based on their temporal relationship with serum iodine concentrations. Our case provides evidence that absorption of iodine after prolonged application of povidone-iodine to a relatively small surface area of denuded skin can result in considerable iodine absorption.

We suggest that an alternate form of therapy be used and that serum iodine determinations be considered in patients receiving topical iodine preparations who display unexplained metabolic abnormalities or organ dysfunction.

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Visual Hallucinations

Clinical Occurrence and Use in Differential Diagnosis

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Visual hallucinations occur in diverse clinical circumstances including ophthalmologic diseases, neurologic disorders, toxic and metabolic disorders and idiopathic psychiatric illnesses. Their content, duration and timing relate to their cause and provide useful differential diagnostic information. Hallucinations must be distinguished from delusions and confabulation. A systematic approach to differentiating among hallucinatory syndromes may improve diagnostic accuracy.

(Cummings JL, Miller BL: Visual hallucinations—Clinical occurrence and use in differential diagnosis. West J Med 1987 Jan; 146:46-51)

Visual hallucinations are common clinical phenomena that occur in a wide variety of ophthalmologic, neurologic, medical and psychiatric disorders. As many as 75% of delirious patients manifest visual hallucinatory phenomena,[1] and when hallucinations dominate the clinical presentation, a patient may be misdiagnosed as suffering from an idiopathic psychiatric disorder. Hallucinations must be differentiated from confabulations and from delusions—syndromes that are also characterized by patient reports that conflict with the experience of clinicians. When hallucinatory syndromes are recognized and their distinguishing characteristics considered, hallucinations may provide considerable differential diagnostic information. In this report we review the definition of visual hallucinations, discuss the clinical significance of hallucinations, review the value of hallucinations in localizing central nervous system (CNS) disturbances and describe the pathogenetic mechanisms responsible for visual hallucinations. A systematic approach to the differential diagnosis of hallucination-producing conditions is presented.

Definition

A visual hallucination may be defined as a visual sensory perception without external stimulation[2] or, more operationally, as a behavioral syndrome in which a patient claims to see something or behaves as if he or she sees something that an observer cannot see.[3] In contrast, delusions are abnormal beliefs that are endorsed by patients as real, that persist in spite of evidence to the contrary and that are not part of a patient's culture or subculture.[2] Hallucinations per se (sometimes called "pseudohallucinations")[4] are recognized as false sensory phenomena, but when they coexist with delusions, a patient may endorse them as real. Hallucinations by themselves are not evidence of psychosis. Confabulation is yet another syndrome where a patient's report is at variance with an examiner's experience. Confabulation involves fabricating facts or events and occurs primarily in patients with memory disturbances.[2] Confabulations typically occur in response to questions probing a patient's orientation or history and do not involve ongoing sensory experience.

Differential Diagnosis

Visual hallucinations can be produced by ophthalmologic diseases, neurologic disorders, toxic and metabolic disturbances, psychiatric disorders and a variety of miscellaneous conditions. Table 1 provides a classification of the causes of hallucinations and presents a framework for the systematic analysis of hallucinatory syndromes.

Among ophthalmologic diseases, total or partial blindness is commonly associated with visual hallucinations. The blindness may be a product of injury to the globe or may be the result of cataract formation, macular degeneration or retinal disease.[3,5-7] Hallucinations associated with blindness have been called "phantom vision" to express their similarity to the phantom-like phenomena following amputation of an extremity. Hallucinations occurring with blindness may be either formed or unformed, but formed hallucinations predominate.[5-7] Unformed hallucinations of ocular origin occur with retinal traction and with glaucoma. Retinal traction gives rise to brief unformed flashes of light as a result of retinal detachment (Moore's lightning streaks) or rapid ocular movement (flick phosphenes).[3,8] Acute glaucoma with a sudden increase in intraocular pressure may result in the appearance of hallu-

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This project was supported by the Veterans Administration.

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
REM = rapid-eye-movement

cinated rainbows surrounding objects. The sudden occurrence of visual hallucinations in the elderly is known as the Charles Bonnet syndrome. Formerly considered an idiopathic disorder, the syndrome has been found to be associated with an occult ocular pathologic disorder in most cases.[9,10] Hallucinatory images arising from ocular disease must be distinguished from entopic phenomena such as opacities in the vitreous humor or seeing elements of one's own retinal circulation (Scheerer's phenomenon).[3,11]

Optic nerve disease gives rise to unformed visual hallucinations when the nerve is inflamed. Patients with optic neuritis frequently experience bright, transient flashes of light when moving their eyes horizontally.[12] This is particularly likely to occur or to be noticed by a patient in a darkened environment or when the eyes are closed. Patients with optic neuritis, optic nerve tumors or arteritis involving the optic nerves may occasionally experience unformed or semiformed hallucinations when startled by sound.[13]

Brain-stem lesions produce a unique type of visual hallucination syndrome known as peduncular hallucinosis. The hallucinations are a product of vascular, neoplastic or other structural involvement of the pons or midbrain and are usually accompanied by disturbances of the sleep-wake cycle and by cranial nerve palsies. The hallucinations typically occur in the evening and consist of geometric patterns, more complex kaleidoscopic scenes of landscapes, flowers, birds, animals or people or visions of miniature animals and beings. The patient may be amused or astonished by the hallucinations and may look forward to their occurrence.[14,15]

Hemispheric lesions may cause ictal hallucinations during the course of a seizure or they may produce "release" hallucinations associated with a visual field defect.[16] Release hallucinations occur with hemispheric infarctions, tumors or other destructive lesions of the geniculocalcarine pathways. The images are often complex regardless of the lesion location, consisting of complex visual patterns or identifiable images of objects, animals or people. They are usually located within the visual field defect, and they may be influenced by environmental factors such as opening, closing or moving the eyes. They are typically novel visual experiences rather than visual memories.[17,18] Release hallucinations are more common with right-sided than with left-sided lesions,[3] and the inciting lesion is often an infarction in the distribution of the right posterior cerebral artery.[17] In the acute stage, release hallucinations persist for as long as several hours per day; they become less frequent and less enduring in the resolution phase of the injury.[19] Figure 1 shows semiformed hallucinations described by a patient who sustained a right occipital infarction (Figure 2).

Ictal hallucinations may be difficult to distinguish from release hallucinations, but a few clinical features help to differentiate the two (Table 2). Ictal hallucinations tend to be brief, stereotyped visual experiences that are not necessarily associated with a visual defect and are frequently not lateralized within the visual field. Ictal hallucinations tend to be unformed when associated with occipital lesions and formed when associated with temporal lobe lesions. The hallucinations produced by temporal lobe foci occasionally consist of visual memories.[20,21] Consciousness may be altered during an ictal hallucination, and some patients have forced head and eye deviation at the time of the hallucination. Visual distortions—metamorphopsia, macropsia, micropsia—sometimes accompany ictal visual hallucinations of temporal lobe origin.[21]

Migraine is a well-known cause of visual hallucinations. Fortification spectra (zig-zag lines, often with an associated scotoma) are the most frequent type of hallucination, but patients who have migraines may experience every variety of hallucinatory image from simple unformed lines and spots to highly complex, formed scenes.[22] Visual distortions, including macropsia and micropsia, may also occur. Such sen-

TABLE 1.—*Causes of Visual Hallucinations*

- Ophthalmologic Diseases
  - Enucleation
  - Cataract formation
  - Retinal disease
  - Choroidal disorder
  - Macular abnormalities
  - Glaucoma
- Neurologic Disorders
  - Optic nerve disorders
  - Brain-stem lesions (peduncular hallucinosis)
  - Hemispheric lesions
  - Epilepsy
  - Migraine
  - Narcolepsy
- Toxic and Metabolic Conditions
  - Toxic-metabolic encephalopathies
  - Drug and alcohol withdrawal syndromes
  - Hallucinogenic agents
- Psychiatric Disorders
  - Schizophrenia
  - Affective disorders
  - Conversion reactions
- Miscellaneous Conditions
  - Dreams
  - Hypnagogic hallucinations
  - Childhood (imaginary companions)
  - Eidetic images
  - Sensory deprivation
  - Sleep deprivation
  - Hypnosis
  - Intense emotional experiences

TABLE 2.—*Features Useful in Distinguishing Ictal and Release Hallucinations Associated With Hemispheric Lesions*

Characteristics	*Ictal Hallucinations*	*Release Hallucinations*
Duration	Brief (usually seconds to minutes)	Persistent (hours)
Variability	Stereotyped content	May be stereotyped, variable or change slowly over time
Visual field defect	Visual field defect may or may not be present	Visual field defect usually present
Lateralization	May or may not be lateralized	Usually lateralized to side of visual field defect
Environmental influence	Little or no response to environmental influences	Frequently influenced by environmental factors, such as opening, moving or closing eyes
Content	May consist of a visual memory	Usually novel
	Tend to be unformed with posterior lesions and formed with temporal	May be formed regardless of lesion location
Associated findings	Consciousness often altered during or after ictal event; head and eye deviation common during hallucination	No associated ictal behaviors or alteration of consciousness

sory distortions have been called the "Alice-in-Wonderland" syndrome, after the tale by Lewis Carroll who called on his own migraine experiences to describe Alice's dramatic changes in size.[23]

Narcolepsy may produce visual hallucinations that are confined to those instants just as one is falling asleep (hypnagogic) or just as one is awakening (hypnopompic). A patient's level of arousal is usually depressed and the hallucinations have a dreamlike quality. The patients may see geometric patterns, landscapes, faces or figures, and there may be associated visual distortions. Hypnagogic hallucinations occur in 15% to 50% of persons with narcolepsy, are often accompanied by sleep paralysis and are a result of intrusions of the dreams of rapid-eye-movement (REM) sleep into wakefulness.[24]

Toxic and metabolic disorders are among the most common causes of visual hallucinations. The hallucinations may be the sole manifestation of the toxic encephalopathy or they may be one expression of a complex delirious state. Visual hallucinations are present in 40% to 75% of patients in metabolic encephalopathies associated with cardiopulmonary insufficiency, uremia, hepatic disease, endocrine disturbances, vitamin deficiency states and inflammatory and infectious diseases.[1] Hallucinations have also been induced by many drugs and toxins including stimulants, antiparkinsonian agents, antidepressants, analgesics and nonsteroidal anti-inflammatory agents, anticonvulsants, cardiovascular agents, antibiotics, hormonal agents and a wide variety of other compounds (Table 3).[1,25-55] In addition to the hallucinations induced during a period of drug ingestion, hallucinations may also be prominent in withdrawal syndromes when the use of alcohol, opiates or sedative-hypnotics is abruptly discontinued.[1] Hallucinogenic compounds routinely capable of producing hallucinations in the absence of delirium include LSD, psilocybin, psilocin, mescaline, harmine, amphetamines, phencyclidine hydrochloride and *Cannabis* derivatives.[25]

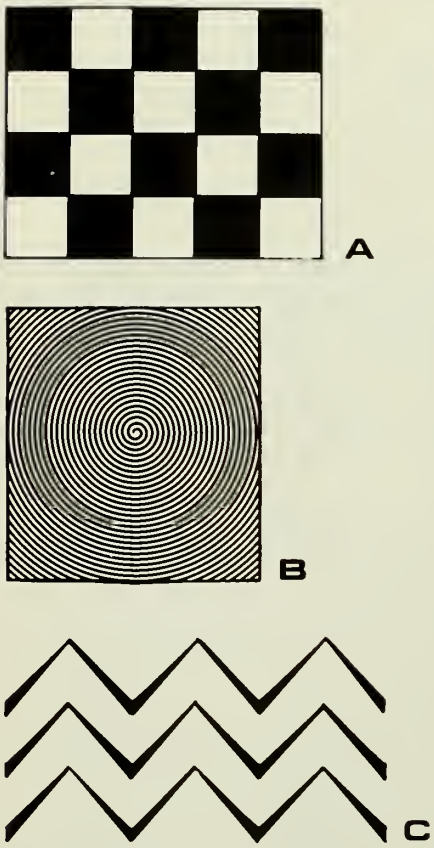

Figure 1.—Visual hallucinations described by a patient with right occipital infarction (computed tomographic scan shown in Figure 2). **A, B** and **C** images appeared sequentially during the first several weeks following the stroke.

Various idiopathic psychiatric disorders can produce visual hallucinations. Hallucinations associated with schizophrenia are primarily auditory in nature, but visual hallucinations occur as a minor symptom in from 24% to 72% of patients at some time during the course of their illness.[56,57] Similarly, auditory hallucinations are the principal type of hallucinatory experience reported by patients with affective disorders, but visual hallucinations are present in 10% of manic-depressive patients at the time of first admission and occur during the course of the illness in as many as 70%.[56,57] Hallucinations occurring with major affective disorders are usually mood congruent, reflecting either the guilty hopelessness of a depressed patient or the expansive grandiosity of mania. Visual hallucinations may also occur as a conversion symptom in patients with conversion reactions.[56,58]

Hallucinations are usually indicative of ocular, neurologic, metabolic or psychiatric disorders, but in some situations they may occur in normal persons; they are not inevitably the harbinger of a disease process. Visual hallucinations are not uncommon in children. Eidetic imagery—the ability to recall visual images with hallucinatory clarity—occurs in some children and less frequently in adults. Children may also have imaginary play objects and companions that they appear to visualize.[59] Dreams are common to all and are visual expe-

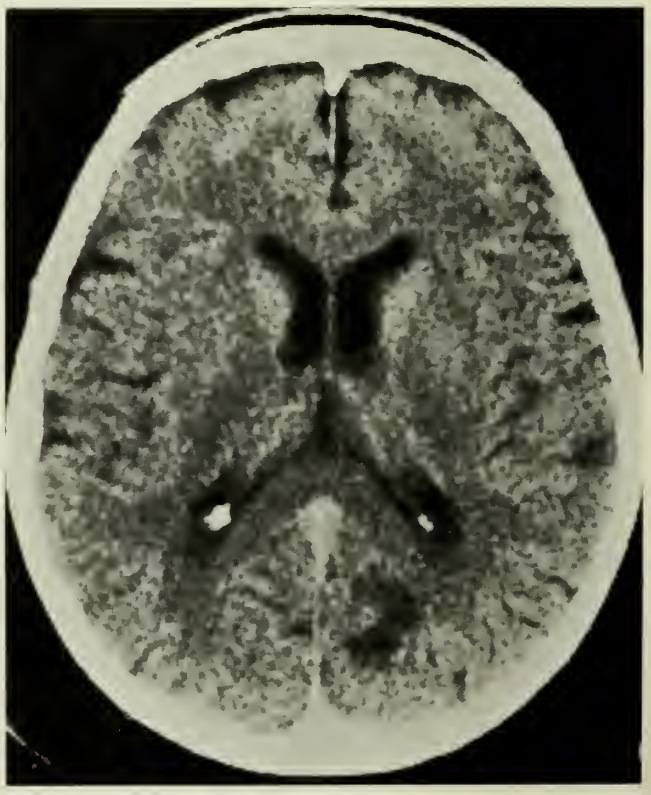

Figure 2.—A computed tomographic scan of a patient with release-type visual hallucinations following a right occipital infarction.

riences included in some definitions of hallucinations. In adults, visual hallucinations may occur during periods of sleep deprivation and sensory isolation or as hypnagogic phenomena unassociated with narcolepsy.[60-62] Hallucinations may also occur as a product of hypnotic suggestion and during the course of intense emotional experiences such as grief reactions. Some cultural groups appear to be more prone than others to hallucinate in stressful circumstances.[63,64] Historically, hallucinations have also occurred in a number of exceptional persons including Socrates, Joan of Arc, Mohammed, Luther, Pascal, William Blake, Bunyan, Napoleon, Raphael and Goethe.[65]

Phenomenology

Distinct varieties of hallucinations have been described and attempts made to correlate them with specific causes or localized regions of brain dysfunction. The most common generalization of this type is to associate unformed hallucinations with occipital lesions and formed hallucinations with temporal lobe injury. As noted above, this rule is most applicable to ictal hallucinations but has little validity for release hallucinations. The latter may be formed images regardless of the location of the lesion. Thus, the characteristics of hallucinations occurring as part of an epileptic seizure may provide important localizing information, whereas other clinical features must be used for localizing lesions associated with release hallucinations.

Not all hallucinations can be adequately described as either formed or unformed. Flashes of light or color are unformed, and complex figures such as animals, people and plants are formed, but many hallucinations have patterned features such as lattices, cones and spirals that are of intermediate complexity. Preliminary cortical stimulation studies suggest that unformed hallucinations are associated with activity of area 17, the primary occipital striate cortex; more patterned hallucinations are associated with dysfunction of area 18, the peristriate visual association cortex; bizarre apparitions such as disengaged objects and people occur with abnormalities of area 19, the more advanced visual association area, and complex remembered visual experiences correlate with medial temporal lobe disturbances.[66]

Lilliputian hallucinations—named after the experiences of Jonathan Swift's character, Gulliver, with the little people of the island of Lilliput[67]—are frequently given special attention in descriptive reports. The patients report seeing tiny but otherwise normally shaped people, animals and objects. Such diminutive figures, however, have been described in a variety of metabolic, neurologic, drug-induced and psychiatric conditions and appear to have no specific localizing or etiologic significance.[18,68,69]

Like Lilliputian hallucinations, autoscopy—the experience of seeing oneself as an hallucinated image—although particularly striking, is without specific focal or etiologic correlates. It has been reported with epilepsy, migraine, cerebral tumors, head trauma, infectious diseases, drug intoxication, schizophrenia and depression.[70,71] Autoscopy figured prominently in several well-known literary works including Edgar Allen Poe's *William Wilson*, Oscar Wilde's *The Portrait of Dorian Gray* and Dostoyevsky's *The Double*.[71]

Geometric "psychedelic" images consisting of checkerboards, spirals and funnels are characteristic of the hallucinations induced by hallucinogenic drugs but are also reported in cases of sensory deprivation and with structural insults to the brain.[60,72,73]

Palinopsia refers to the persistence or recurrence of visual images after the exciting stimulus has been removed.[74] A patient views an object, and the image is retained for 20 to 60 seconds after the gaze is redirected. The image may spontaneously recur for a period of up to several hours after the initial experience. Palinopsia is a special variant of release hallucination, occurring primarily in patients with visual field defects and right-sided posterior hemispheric lesions.[75]

Distinctions are usually made between hallucinations, where the perception is independent of a stimulus object, and illusions, where there is a distortion of an existing environmental stimulus. Clinically, however, the two phenomena frequently co-occur and have been reported together in pa-

TABLE 3.—*Drugs Associated With Visual Hallucinations*

- Hallucinogens
  - Dimethyltryptamine
  - Harmine
  - Ketamine hydrochloride
  - LSD
  - Mescaline
  - Nitrous oxide
  - Phencyclidine hydrochloride (PCP)
  - Psilocybin
  - Tetrahydrocannabinol
- Stimulants
  - Amphetamine
  - Cocaine
  - Methylphenidate
- Antiparkinsonian Agents
  - Amantadine hydrochloride
  - Anticholinergic drugs
  - Bromocriptine
  - Levodopa
  - Lisuride
  - Mesulergine
  - Pergolide mesylate
- Antidepressants
  - Amitriptyline hydrochloride
  - Amoxapine
  - Bupropion hydrochloride
  - Doxepin hydrochloride
  - Imipramine hydrochloride
  - Lithium carbonate
  - Phenelzine sulfate
- Anticonvulsants
  - Ethosuximide
  - Phenobarbital
  - Phenytoin
  - Primidone
- Cardiovascular Agents
  - Digitalis
  - Disopyramide
  - Methyldopa
  - Propranolol hydrochloride
  - Quinidine
  - Reserpine
  - Timolol
- Antibiotics
  - Antimalarial agents
  - Cycloserine
  - Isoniazid
  - Podophyllum resin
  - Procaine penicillin
  - Sulfonamides
  - Tetracycline
- Hormonal Agents
  - Levothyroxine sodium
  - Steroidal agents
- Analgesics and Nonsteroidal Anti-inflammatory Agents
  - Indomethacin
  - Nalorphine
  - Narcotic agents
  - Pentazocine
  - Phenacetin
  - Salicylates
- Miscellaneous Agents
  - Baclofen
  - Bromide
  - Cimetidine
  - Clonazepam
  - Diethylpropion hydrochloride
  - Disulfiram
  - Ephedrine
  - Heavy metals
  - Hexamethylamine
  - Metrizamide
  - Phenylephrine hydrochloride
  - Promethazine hydrochloride
  - Ranitidine
  - Solvents
  - Vincristine
  - Volatile hydrocarbons

tients with epilepsy, migraine, narcolepsy and in toxic and metabolic conditions.[23,24,64,72] Their occurrence in the same clinical disorders suggests that they may arise from similar neurophysiologic alterations.

Mechanisms of Hallucinations

Despite the wide variety of clinical circumstances in which visual hallucinations may occur, most cases can be attributed to a few basic pathogenetic mechanisms. A common situation in which hallucinations emerge involves reduced visual input. Thus, hallucinations occur with sensory deprivation, enucleation, cataract formation, retinal disease, choroidal disorder or macular degeneration and with optic nerve lesions. Reduced visual stimulation is also present in the release hallucinations associated with hemispheric damage involving the geniculocalcarine pathways and producing homonymous visual field defects. Deprivation of visual input produces visual hallucinations with similar characteristics, and West proposed a "perceptual release theory" suggesting that diminished sensory input results in a release of spontaneous activity within CNS structures normally responsible for mediating perceptual phenomena.[76] The disinhibited sensory activity induces hallucinations within the appropriate sensory sphere. This basic mechanism might also account for hallucinations associated with diminished arousal in narcolepsy, hypnotic and trance states, confusional disorders and some idiopathic psychiatric disturbances as well as those associated with clinically unmistakable visual-sensory loss.

Abnormalities of sleep and dreaming also account for many cases of visual hallucinations. Hypnagogic and hypnopompic hallucinations of narcolepsy occur when the dreams of REM sleep intrude into wakefulness.[24] Dream intrusion also appears to account for the visual hallucinations associated with withdrawal from alcohol and sedative agents, the long-term use of which suppresses REM sleep and produces a rebound of excessive REM activity during withdrawal periods.[77] A diurnal schedule of peduncular hallucinosis suggests that the syndrome may also be related to sleep and dream mechanisms.[14,15]

Ictal hallucinations represent a distinct pathophysiologic variety of visual hallucinations. Spontaneous or iatrogenic stimulation of the occipital cortex may produce unformed hallucinations and stimulation of the temporal cortex often produces formed hallucinatory images. The tendency for both ictal and release hallucinations to arise from lesions in the right hemisphere correlates with the nonverbal visuoperceptual specialization of the right brain.

Several mechanisms have been proposed to explain the hallucinations induced by hallucinogenic agents.[25] LSD is among the most powerful of hallucinogens and has effects on serotonergic and limbic system structures. It has both agonist and antagonist properties in serotonergic systems and may interfere with serotonin-dependent raphe nuclei that regulate REM sleep.[78] A role for the limbic system in LSD-induced hallucinations is suggested by the observation that LSD phenomenology is diminished following temporal lobectomy.[79] Noradrenergic and dopaminergic agents causing hallucinations also appear to exert their actions on limbic and brainstem structures, whereas hallucinations associated with taking anticholinergic agents and overdoses of other drugs are usually part of a delirious state.

Thus, most hallucinations can be correlated with a few basic mechanisms—perceptual release, ictal discharges, dream intrusion or neurochemical effects on brain-stem and limbic system structures.

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Occult Carbon Monoxide Poisoning

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A syndrome of headache, fatigue, dizziness, paresthesias, chest pain, palpitations and visual disturbances was associated with chronic occult carbon monoxide exposure in 26 patients in a primary care setting. A causal association was supported by finding a source of carbon monoxide in a patient's home, workplace or vehicle; results of screening tests that ruled out other illnesses; an abnormally high carboxyhemoglobin level in 11 of 14 patients tested, and abatement or resolution of symptoms when the source of carbon monoxide was removed. Exposed household pets provided an important clue to the diagnosis in some cases. Recurrent occult carbon monoxide poisoning may be a frequently overlooked cause of persistent or recurrent headache, fatigue, dizziness, paresthesias, abdominal pain, diarrhea and unusual spells.

(Kirkpatrick JN: Occult carbon monoxide poisoning. West J Med 1987 Jan; 146:52-56)

Although acute carbon monoxide (CO) poisoning is a well-described clinical condition, chronic CO poisoning is a seldom-recognized and poorly understood clinical disorder. I report a surprising incidence of 26 cases in two years in a general internal medical practice and present clinical and laboratory observations.

Patients and Methods

Patients included in this report sought care between 1982 and 1984 for fatigue, headache or at least two of the symptoms listed in Table 1. Criteria for their inclusion in the series were having had symptoms for at least one month and improvement in their condition after a source of CO in their environment was removed. Urine and blood specimens from the principally exposed person in each family were used for routine screening tests—complete blood count, erythrocyte sedimentation rate, a battery of chemistry tests and urinalysis. A patient's carboxyhemoglobin level was measured as soon as possible after the suspected CO exposure. Of 32 patients and family members given questionnaires regarding defective equipment, duration of symptoms before diagnosis and recovery time, 25 returned the questionnaires. Also included in the report are four patients with symptoms who had had furnace problems, had heard about the study and volunteered to fill out questionnaires. In these instances, no tests were done and carboxyhemoglobin levels were unknown because the faulty source of CO had already been repaired. Three patients were eliminated from the study because they had symptoms that persisted more than six months after the suspected source of CO had been repaired. The profile of the 26 patients is given in Table 2.

Household pet morbidity and mortality were also surveyed because patients frequently told us of bizarre pet behavior and death (Table 3). Six pets had died and six others had had symptoms conceivably related to CO exposure.

A causal association between CO exposure and clinical illness is suggested by case histories, identifying a CO source, carboxyhemoglobin levels exceeding normal values (less than 3% for nonsmokers) and symptom resolution on repair of the CO source. The exact quantity of CO was measured in a patient's environment in one case, and in most other cases a mechanic or repairer found a cracked heat exchanger, a faulty muffler or a plugged furnace exhaust chimney. The defective equipment was repaired after atmospheric screening devices (for example, Drager tubes) registered unsafe concentrations of environmental CO.

Results

Questionnaire results are shown in Tables 1 through 3. In this series of 26 cases, 15 patients were exposed to 9 defective gas furnaces, 3 to faulty oil furnaces, 7 to malfunctioning automobile exhaust systems and 1 to a defective bus exhaust system. The exhaust system defects were found in mufflers, catalytic converters and a gas manifold (Tables 1 through 3).

Carboxyhemoglobin Levels

Carboxyhemoglobin levels were measured in blood specimens of 14 patients within five hours of suspected CO exposure. The concentrations ranged from 8.8% to 36.8% (mean 15.1%). The mean concentration for patients exposed to an automobile with exhaust problems was 14.0% and that for patients exposed to a faulty furnace, 15.8%. Three patients with chronic symptoms presented in coma; all three had nat-

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ural gas furnaces. (They are included in this report as having long-term exposure because their symptoms were present for several days to weeks before the episodes of unconsciousness began.)

Symptoms

Most patients reported fatigue and headache (Table 1). A majority also reported having trouble thinking, dizziness, a pounding heart and shortness of breath. Nine patients had impaired visual acuity; it was the initial complaint in three patients. Diarrhea and abdominal pain were also frequently described, as were chest pain, paresthesias and "vague spells."

TABLE 1.—*Frequency of Symptoms in Patients Exposed to Carbon Monoxide (26 Patients)*

Symptom	Patients Number	Patients Percent
1. Fatigue	24	92
2. Headaches	22	85
3. Trouble thinking	20	77
4. Dizziness	19	73
5. Nausea	15	65
6. Trouble sleeping	15	65
7. Heart pounding	14	54
8. Shortness of breath	14	54
9. Numbness or tingling	12	46
10. Chest pain	9	35
11. Decreased vision	9	35
12. Diarrhea	9	35
13. Unusual spells	9	35
14. Abdominal pain	7	27

Illustrative Cases

Cases 1 through 6. Patient 1, a 34-year-old mother of three, presented with persistent fatigue, headache, hearing loss, sinus congestion and chest pain. Symptoms had begun the previous winter but had abated slightly during the summer. In October and November her fatigue, headache and lightheadedness precluded all volunteer work, housework and cooking. Family members were initially unaffected.

On physical examination she had mild hypertension (blood pressure 140/100 mm of mercury). Values for urinary excretion of catecholamines were 118 μg per 24 hours (normal 30 to 100) and vanillylmandelic acid, 10.76 mg per 24 hours (normal 1 to 8). Results of a repeat study of a 24-hour urine collection during the hospital stay were normal, as were concentrations of plasma catecholamines. A computed tomographic scan of the abdomen was also normal, and she was discharged with no diagnosis.

Meanwhile her mother, who was staying with the family to help with household chores, began to feel fatigued, hypersomnolent and complained of acroparesthesias. When the gas furnace in the home was checked, a CO leak was detected in

TABLE 2.—*Patient Profile**

Patient	Age, Yr	Sex	Smoker	Symptoms†	Duration of Symptoms, Months	Occupation	Carboxy-hemoglobin Level, Percent	Source of CO	Time Until Symptoms Resolved, Weeks
1	34	♀	Yes‡	1-14	3	Homemaker	8.8	Gas furnace	4-6
2	39	♂	No	1-3,6-9,11,12	3	Accountant	15.8	Gas furnace	2-4
3	8	♀	No	1-6,10,14	3	Student	5.0	Gas furnace	2-4
4	8	♀	No	1-4,6,10	3-6	Student	3.5	Gas furnace	2-4
5	5	♂	No	1-6,7,9,12,14	3-6	Student	7.8	Gas furnace	2-4
6	53	♀	No	1-4,6,8-11,13,14	3-6	Homemaker	NC	Gas furnace	4-8
7	57	♂	Yes	1,4-6,8,9,12	6	Stevedore	19.0	Gas furnace	4-6
8	29	♂	No	1-14(coma)	1	Carpenter	25.9	Gas furnace	12
9	28	♀	No	1-8,11-13(coma)	1	Veterinarian's assistant	19.8	Gas furnace	2-8
10	61	♀	No	1-3,6,7	<1	Homemaker	36.8	Gas furnace	12
11	62	♂	No	1,2,4,5,7,8,12	<1	Physician	NC	Gas furnace	1
12	47	♂	No	2,6,8,10	3	Army officer	NC	Gas furnace	1
13	41	♀	No	1-3,8,10	6	Office worker	NC	Gas furnace	2-4
14	30	♂	No	1-7,9	3	Accountant	1.5§	Gas furnace	4
15	33	♀	No	1,2,5-7,9	1	Research technician	NC	Gas furnace	1-2
16	25	♀	No	1-3,5,6,12,13	3	Nurse	1.0§	Oil furnace	2-4
17	61	♀	No	1,2,4,7	6	Homemaker	3.3§	Oil furnace	2
18	34	♀	No	1-11,13,14	3-6	Homemaker	3.0§	Oil furnace	12
19	43	♀	No	1-4,8,12	>6 (4 yrs)	Psychologist	8.8	Auto muffler/hatchback door	>8
20	26	♀	Yes	1-5,8	12	Receptionist	2.8§	Auto exhaust manifold	8
21	36	♀	No	3,4,11	1	Teacher	22.0	Auto exhaust recycler	<1
22	36	♀	No	1-11,13,14	6	Beautician	16.3	Auto catalytic converter	12
23	27	♀	No	1,3-5,7,12-14	6	Attorney	21.9	Auto catalytic converter	2
24	30	♀	No	1-5,8-10,13	1	Medical assistant	11.0	Auto exhaust manifold	4-8
25	27	♂	No	1	3	Medical student	NC	Auto muffler	1
26	42	♀	No	1-4,7-9,11,13	1	School bus driver	NC	Bus tailpipe	4

CO=carbon monoxide, NC=not checked

*Patients 1 to 5 are in the same family, patients 8 and 9 are married and patients 10 and 11 are married.
†Symptoms numbered as in Table 1.
‡5 cigarettes per day.
§Blood sample drawn >24 hours after exposure to CO.

TABLE 3.—*Sick Pets in Households of People Exposed to CO*

1 Dead canary
4 Dead puppies
1 Dead cat
2 Cats behaving strangely ("potty trained until period of exposure")
3 Dogs behaving strangely ("lethargic, would not lie on floor, spacey")
1 Dog with diabetes insipidus (polyuria, polydypsia)

the heat exchanger. Carboxyhemoglobin levels in the patient (who smoked four to five cigarettes a day), her husband (a nonsmoker) and their twin daughters and son were 8.8%, 15.5%, 7.5%, 5.0% and 3.5%, respectively.

Her husband (patient 2), an accountant, noted an inability to commit figures to memory and difficulty with dictation, which he attributed initially to "the stress of my wife's illness." Their 8-year-old twins (patients 3 and 4) had not felt well, and their 5-year-old son (patient 5) had been having school problems, headaches, dizziness and fatigue.

COMMENT. The severity of the illness seemed to correlate with the relative exposure to the contaminated environment. In this family, the mother (patient 1) and youngest child, who spent more time at home, had more severe symptoms than the father and older children.

Cases 8 and 9. A 29-year-old male carpenter and his 28-year-old wife (a veterinarian's assistant) came to an emergency room with headache, fatigue, nausea, weakness, dizziness, shortness of breath, chest pain and diarrhea of a week's duration. Initial evaluation led to a presumptive diagnosis of a viral illness. Two days later they were seen in an outpatient clinic with progressive symptoms and were given the same diagnosis. The next day the symptoms became excruciating (headache, weakness, vomiting and diarrhea). They returned to the emergency room and were again sent home with a diagnosis of "the flu." During this time, three of their one-month-old puppies had died, and an autopsy showed "pulmonary consolidation and emphysema." In retrospect the couple noted that their symptoms decreased when they were away from home.

Two days later, when the couple did not keep an engagement, the host became concerned and found them comatose at home, their last puppy dead, one adult dog unconscious and another dog aimlessly wandering around the house. The fire department was called and found their furnace chimney clogged with soot. The couple was given oxygen and taken to a local emergency room. Carboxyhemoglobin levels determined from blood specimens drawn after an undetermined interval of oxygen administration were 19.8% for patient 9 and 25.9% for patient 8. They were transferred to the Virginia Mason Hospital (Seattle) Hyperbaric Unit for treatment of their acute and chronic CO poisoning. They were lethargic, confused and ataxic and complained of nausea and severe headache on arrival. Symptoms abated with administration of hyperbaric oxygen, but persistent ataxia and headache, plus bilateral subhyaloid hemorrhages in the woman, necessitated a second hyperbaric treatment the following day.

Patient 8's course was complicated by a deep venous thrombosis and pulmonary infarct four days later. He also continued to have minor difficulties with balance, requiring a change in job from high-rise scaffold carpentry. Patient 9 recovered completely after several weeks of mild headaches and visual disturbances.

COMMENT. The health of household pets can provide an important diagnostic clue in an otherwise obscure illness. When several family members are ill simultaneously and household pets are more severely affected, the type and condition of heating appliances should be determined.

Case 23. The patient, a 27-year-old female attorney, saw her physician because of a syncopal spell. She said she experienced episodes of palpitations, weakness, severe fatigue, nausea and lightheadedness almost daily at work, usually following afternoon coffee breaks. She was a nonsmoker, but others in the staff lounge smoked. When tests were done on serum specimens taken during such an attack, her blood glucose level was 85 mg per dl (normal 75 to 115) and her carboxyhemoglobin concentration was 21.9% (normal less than 3%). The source of CO was a faulty catalytic converter in her car. Repair of the defect resulted in complete resolution of her symptoms within two weeks.

COMMENT. Patients who receive repeated sublethal doses of CO probably accumulate CO in body tissues. In this patient, small additional subsequent exposures from bus fumes and cigarette smoke may have been enough to provoke symptoms. Laboratory results from blood specimens obtained during an attack eliminated the possibility of hypoglycemia and established the diagnosis.

Discussion

More than 3,800 people die annually of carbon monoxide poisoning and at least 10,000 miss at least one day of work because of a sublethal exposure.[1] Considering how obvious the existence of a toxic environment seems once a CO source is found, one must consider why repeated occult CO exposure is seldom recognized. The index cases in our series were a family of five in a home with a faulty gas furnace. The wife, a homemaker with ongoing exposure to CO, became almost completely disabled. The husband's work performance declined, and the children's school work deteriorated. The family members' vague symptoms and impaired cognition initially misled their physicians. After her condition improved in hospital, the mother had a relapse. Only when other family members home for Christmas vacation began to note similar symptoms and when symptoms developed in the patient's mother after she came to stay with the family was the correct diagnosis of a toxic home environment made.

Diagnosis

Suspected chronic CO poisoning is difficult to document in the office. Ascertaining the carboxyhemoglobin level is the only way to quantitate exposure. No test of tissue levels of CO is available, though this information may be more closely related to the severity of symptoms than the carboxyhemoglobin level.[2] Carboxyhemoglobin determination is limited in usefulness because it correlates poorly with symptoms and it decreases in sensitivity as an indicator of CO poisoning as the time from last exposure approaches four hours because of carboxyhemoglobin's rapid clearance. Its half-elimination time in room air is about five hours, in 100% oxygen two hours and with hyperbaric oxygen only 23 minutes.[3]

Promptly collecting a serum specimen after exposure is, therefore, a critical factor in interpreting the carboxyhemo-

globin level. But if 100% oxygen has been administered to a comatose patient for one hour in the ambulance during transport and the car in which the patient tried to commit suicide has run out of gas, a carboxyhemoglobin level of 5% or less should not rule out the diagnosis of CO poisoning.

To further confound interpretation, carboxyhemoglobin levels are increased in smokers; a smoking history must be taken into account when interpreting the test results. According to the National Bureau of Health Statistics,[4] 98% of nonsmokers have a blood level of less than 2%. A smoker, whose carboxyhemoglobin level may be 10% to 15% after smoking, has no symptoms most of the time, perhaps because he or she gets a reprieve between cigarettes and during the night. The carboxyhemoglobin measurements of four smokers in this series ranged from 19.0% and 8.8% when tested within the four-hour period, down to 3.0% and 2.8% for two tested eight hours and seven days after exposure, respectively. These latter two measurements reflect the background level of CO exposure or endogenous production for these patients, rather than the exposure related to their increased symptoms. Obviously, smoking is a confounding variable and must be considered in evaluating the carboxyhemoglobin level.

Symptoms have failed to correlate well with the level of carboxyhemoglobin. For example, there are reports of patients with severe exposure (coma) who have carboxyhemoglobin levels of zero.[5] Others have levels in the 20% to 30% range with minimal symptoms. Patients in this series with long-term daily exposure may have many symptoms and yet have levels—5% to 15%—that are considerably lower than the arbitrary value set by the standard symptom tables.[6] These tables have been derived from cases of sudden and intense exposure and, even in that context, individual symptoms are highly variable at moderate to high levels of carboxyhemoglobin. The correlation of blood CO levels with the symptoms of patients with daily sublethal exposures is not known.

Confirming a diagnosis requires identifying an exposure source, compatible symptoms and prompt carboxyhemoglobin determination. Under these conditions, lower levels of carboxyhemoglobin, such as 5% to 15%, should be accepted as evidence of CO toxicity, but just what these values should be remains uncertain.

Controlled studies comparing air quality in homes and vehicles with carboxyhemoglobin levels of the occupants (with specimens drawn at the site) are not yet available, nor did we address this important issue. This testing requires suitable equipment and staff to go to the site, resources not available for this series. Patients made their own arrangements with utilities personnel to help investigate the condition of home heating systems.

Sources of CO

When an elevated level of carboxyhemoglobin is found, it can reflect a wide range of sources of CO, including combustion gases, cigarettes and absorption of a solvent that metabolizes to CO. Virtually any indoor appliance in which a fuel is burned without adequate ventilation can be a source of lethal or sublethal CO poisoning. Grace and Platt[7] reported the cases of two patients with myocardial infarction and pulmonary emboli who were exposed to carbon monoxide from a defective natural gas water heater and furnace. Fisher[8] reported the cases of 12 patients exposed to four kerosene space heaters. Stewart and Hake[9] implicated methylene chloride (the active solvent in paint strippers and carburetor cleaners) as the precipitating factor in two cases of fatal myocardial infarction. Sterno (canned fuel) used in a high school chemistry laboratory was responsible for multiple symptoms in several students.[10] Charcoal briquettes and pressed woodchip logs producing relatively smokeless fires generate large amounts of CO.[11] Aronow and Isbell pointed out that vehicle exhaust may have favored an onset of angina in patients exposed to Los Angeles freeway traffic.[12] Ice skaters and hockey players have also had symptoms from exposure to the exhaust of faulty ice-resurfacing machines.[13]

Wood, oil and kerosene are all possible sources of CO when there is inadequate oxygen available for combustion. The combustion of these fuels usually also produces irritating smoke that alerts the potential victim, but not invariably. Several of the patients in this series were unaware of such exposure when it occurred.

A special problem exists with gas appliances. Although natural gas burns most efficiently and most cleanly compared with other forms of fuel, it is also the most potentially lethal.[14] Of 340 CO deaths reported in 1982 by the US Consumer Product Safety Commission, 290, or 85%, were due to gas appliances. A major medical textbook is misleading when discussing CO poisoning. The statement, "much higher concentrations [of CO] are present in most illuminating and heating gases, but not in natural gas,"[15] although true, does not go the necessary step further to say "unless combustion is incomplete." In circumstances of inadequate ventilation or a defective exhaust pathway, natural gas appliances may emit potentially lethal CO *without any irritating fumes.* Therefore, natural gas appliances must be treated with utmost caution, and all suggested maintenance schedules must be followed. When unusual symptoms occur in patients who use gas appliances and these symptoms worsen during the heating season, appliances should be inspected.

Vehicle exhaust is the most common source of CO-induced morbidity and mortality. In particular, children who lie down in the rear of station wagons may be affected, even when the occupants of the front seats have no symptoms.[16] Faulty exhaust systems in cars, buses and trucks may also account for chronic symptoms of headache, dizziness, drowsiness, nausea, visual disturbances and fatigue. The incidence is unknown but probably substantial.

The use of catalytic converters (which convert carbon monoxide to carbon dioxide and water)[17] and emissions control testing, mandatory for vehicle license renewal in certain cities with excessive air pollution, have been helpful in reducing atmospheric CO content and identifying problem vehicles. Older cars that are not required to be tested, however, represent a potential CO source that remains undetected by current emission testing.

Finally, cigarette smoke is another source of CO and represents a hazard to the active smoker, to the passive bystander and, during a smoker's pregnancy, to the fetus.[18]

Pets

The effect of carbon monoxide on animals (see Table 3) deserves special comment. Miners used to take canaries or mice down mineshafts before CO detectors were available. If

the bird or animal died, they knew that levels of CO were high.

Physicians often inquire about recent travel or whether there are sick animals in the houses of patients with vague complaints. Their thoughts, however, usually revolve around transmission of infection through contaminated food and water sources or infected animals. Household pets are apt to be more severely affected than their owners by domestic carbon monoxide as they have smaller muscle mass, higher metabolic rates and may be indoors 24 hours a day. An autopsy diagnosis such as "pulmonary consolidation and emphysema" in the mysterious deaths of several four-week-old puppies in cases 8 and 9 should bring to mind the possibility of an environmental toxin such as carbon monoxide, particularly in a gas-heated home where the humans are also feeling ill.

Carbon monoxide poisoning might easily be misdiagnosed as "a viral syndrome," particularly during the home heating season. Transmission of infection from household pets to humans and vice versa does occur,[19] but the common "flu-season" viruses are not transmitted between pets and owners. Therefore, any unusual behavior or illness in domestic animals may provide a clue to the correct diagnosis.

Differential Diagnosis

The most common symptoms of any CO exposure are headache and fatigue, which, along with dizziness, nausea, trouble thinking and concentrating, palpitations and sleep disturbance, can be symptoms of depression. Clues that help differentiate CO poisoning from depression and other conditions are the health of pets and other family members, a negative social history and the presence of other unusual symptoms. Impaired visual acuity, which was the presenting complaint in three patients, should alert a clinician to the possibility of CO poisoning if a potential source is present.

In our series, a third of the patients had diarrhea and abdominal pain, symptoms not commonly associated with a diagnosis of CO poisoning. A plausible mechanism is hypoxia of the intestinal mucosa.

The workup for a patient with "spells" or syncope does not traditionally include questions about environmental CO sources or a test of the carboxyhemoglobin level. The frequency of this complaint in our patients (35%) suggests occult CO poisoning as a possible cause in the undiagnosed case.

Finally, CO poisoning is most frequently misdiagnosed as a viral syndrome. Distinguishing features of CO poisoning are the absence of myalgias, fever, sore throat and adenopathy; simultaneous illness in homebound family members and pets, and improvement with exposure to fresh air.

Nonspecific vague symptoms such as in this series often represent functional illness rather than CO poisoning. A causal association is supported, however, by finding a source of carbon monoxide in the home, workplace or vehicle; negative screening tests for other illnesses; an abnormal carboxyhemoglobin level in 11 of 14 patients, and abatement or resolution of symptoms when the source of carbon monoxide was removed. Furthermore, none of these patients have since reported recurrent symptoms.

Conclusion

The historical findings that should trigger an investigation of possible CO sources are persons whose occupations expose them to vehicle exhaust; households where people and pets are all feeling less well than usual; persons who use solvents containing methylene chloride, including paint strippers and carburetor cleaners, and anyone who has several of the symptoms associated with ongoing CO exposure.

The problem of CO accumulation in homes may become more frequent as more people insulate their homes. In the Pacific Northwest, where electric heat has long been much less expensive than other heat sources, electric power is now rising in cost. Many homes may be converted to using combustion fuels, with greater potential for CO leaks. Clinicians in other areas where higher priced electricity is seldom used for heating may already be seeing a significant number of patients with CO exposure not caused by smoking.

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Medical Progress

Gastrointestinal Manifestations of the Acquired Immunodeficiency Syndrome

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In addition to abnormalities in systemic immune function, patients with the acquired immunodeficiency syndrome (AIDS) and the pre-AIDS syndromes have significant abnormalities in the distribution of T-cell subsets in the intestinal tract. Such immune deficits predispose such patients to opportunistic infections and tumors, many of which involve the gastrointestinal tract. For example, Candida albicans *often causes stomatitis and esophagitis. Intestinal infections with parasites (*Cryptosporidium, Isospora belli, *Microsporidia) or bacteria (*Mycobacterium avium-intracellulare*) are associated with severe diarrhea and malabsorption, whereas viruses like cytomegalovirus and herpes simplex virus cause mucosal ulcerations. Clinically debilitating chronic diarrhea develops in many AIDS patients for which no clear cause can be identified. Enteric pathogens like* Salmonella *and* Campylobacter *can be associated with bacteremias. Kaposi's sarcoma and lymphoma involving the intestinal tract are now well-recognized complications of AIDS. Although AIDS is not associated with a pathognomonic liver lesion, opportunistic infections and Kaposi's sarcoma or lymphoma may involve the liver.*

(Rodgers VD, Kagnoff MF: Gastrointestinal manifestations of the acquired immunodeficiency syndrome [Medical Progress]. West J Med 1987 Jan; 146:57-67)

The acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a retrovirus that is lymphotropic for T cells.[1,2] This virus specifically attacks and depletes the T-helper-cell population.[3] Because of the central role of T-helper cells in the regulation of other components of the cellular immune system, infection with HIV indirectly impairs a broad array of immune reactions.[4] Documented immunologic abnormalities in AIDS have included lymphopenia,[5] a decrease in the ratio of T-helper to T-suppressor cells,[6] a decreased number of T-helper cells,[7] depressed T-cell blastogenesis to mitogens and antigens,[8] diminished cytotoxic cell responses,[9] impaired lymphokine production,[10] defects of monocyte chemotaxis and phagocytosis[11] and activation of B cells with resultant polyclonal gammopathy.[12] These abnormalities, alone and in combination, impair a host's immunocompetence and render the host susceptible to the development of severe opportunistic infections and rare malignant conditions.[13] In AIDS, almost every organ system including the gastrointestinal tract has been involved with unusual infections and malignant disorders. In this paper, we review the immunologic and clinical manifestations of HIV-induced disease in the gastrointestinal tract.

The Intestinal Immune System

Homosexual men have an increased incidence of sexually transmitted enteric infections,[14] and, in patients with AIDS, severe intestinal infections with unusual organisms such as *Cryptosporidium, Isospora belli* and *Mycobacterium avium-intracellulare* have been reported.[15] We recently examined changes in the distribution of T cells and other mononuclear cells in the intestinal tract of groups of homosexual men, including those with AIDS.[16] None of these men had chronic diarrhea at the time of evaluation, although many did have a history of diarrhea. Subjects were stratified into four groups: healthy homosexual men, homosexual men with the lymphadenopathy syndrome or those with AIDS and healthy heterosexual controls.

As summarized in Table 1, mononuclear cells were significantly increased in the small intestinal mucosa of persons with AIDS and the lymphadenopathy syndrome. In contrast, the same persons had a significant decrease in total T cells in

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This study was supported in part by Universitywide Task Force on AIDS.

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV = human immunodeficiency virus
HSV = herpes simplex virus

the intestinal mucosa. This decrease most severely affected the T-cell subset identified by the Leu 3a monoclonal antibody that recognizes the CD4 antigen on T-helper/inducer cells (Figure 1). In addition, subjects with the lymphadenopathy syndrome and with AIDS had a significant decrease in the ratio of mucosal and circulating helper/suppressor T cells (Table 1, Figure 2). The proportion of mucosal T cells identified by Leu 2a, a monoclonal antibody that recognizes the CD8 antigen on cytotoxic/suppressor T cells, was significantly increased only in AIDS subjects (Table 1). In healthy homosexual men the ratio of mucosal helper/suppressor T cells was normal, but the circulating ratio was decreased (Table 1, Figure 2). These findings suggest that mucosal immune abnormalities may contribute to the development of intestinal and systemic opportunistic infections and perhaps to neoplastic disease in patients with HIV-induced disease. Although it was suggested that a decreased number of immunoglobulin A plasma cells in the intestinal mucosa of patients with AIDS may predispose them to infection,[17] a decreased number of IgA plasma cells was not found in the above group of homosexual men with AIDS (D. Kaiserlian, PhD; V. Rodgers, MD, and M. Kagnoff, MD, unpublished observations, July 1985).

Candida albicans

Candida albicans is a frequent opportunistic infection in immunocompromised hosts. Gastrointestinal infection in such persons can involve various mucosal surfaces.[18] *Candida* esophagitis, but not oral candidiasis, is an opportunistic infection that meets the surveillance criteria for AIDS.

Oral candidiasis often is a harbinger for the subsequent development of AIDS in persons at high risk, and such patients may have severe immune deficits.[19] Oral lesions occur as patchy pseudomembranes or ulcers that are painful and debilitating.[20] Recommended treatment includes administering clotrimazole troches, five times per day for seven to ten days, or nystatin suspension, 500,000 units four to six times a day.[20] Patients whose lesions are refractory to this therapy may be given ketoconazole, 200 to 400 mg daily for ten days.

Candida esophagitis is seen frequently in patients with AIDS.[21(pp101-103)] Odynophagia, dysphagia and burning associated with swallowing are common symptoms. Patients occasionally present with upper gastrointestinal tract bleeding or esophageal perforation. Diagnosis using radiographic techniques can be difficult because of the superficial nature of the mucosal abnormality. Even with the use of double-contrast barium studies of the esophagus (Figure 3), a sensitivity of only 80% is achieved.[22] Typically, x-ray films show mucosal plaques that consist of raised areas of necrotic epithelial debris or actual colonies of the organisms. These plaques may be diffuse and produce linear or irregular filling defects with intervening segments of normal mucosa. Clinically unmistakable ulcerations may be seen with more dense disease. Unfortunately, the radiographic appearance is not specific and can be mimicked by various other lesions including reflux esophagitis, herpes simplex esophagitis and cytomegalovirus esophagitis.

Endoscopic evaluation and biopsy are required to confirm a diagnosis of *Candida* esophagitis. Esophagoscopy typically shows linear ulcers and overlying exudate that usually is distributed throughout the esophagus.[23] Biopsy specimens showing acute and chronic inflammation with the presence of mycelia are diagnostic.[23]

One study of ketoconazole therapy in AIDS patients with *Candida* esophagitis showed poor resolution, even with as long as six months of therapy, although patients did note symptomatic improvement.[24] Oral lesions may resolve despite the persistence of esophageal lesions. Thus, neither resolution of symptoms nor oral lesions can be used to judge the efficacy of therapy. Short courses of amphotericin B at doses of 100 to 150 mg given intravenously for five to seven days are recommended for refractory cases. Topical therapy for *Candida* esophagitis is not adequate.

Candida enteritis is rare in patients with AIDS, with only one case reported.[25] That patient presented with watery diarrhea and oral and anal involvement with candidiasis. Small bowel radiographs revealed a dilated ileum with mildly thickened folds. Perforation and peritonitis subsequently developed. On autopsy extensive ulceration of the ileum due to *Candida* and multiple sites of perforation were noted. Disseminated candidiasis has been reported in patients with underlying malignant disorders and neutropenia and frequently

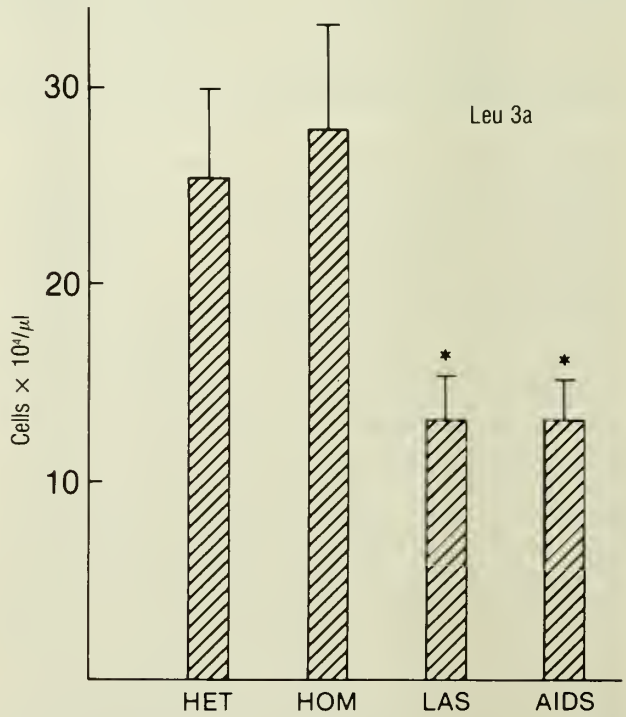

Figure 1.—Phenotypic analysis of intestinal mucosal lymphocyte populations using the Leu 3a monoclonal antibody in healthy heterosexual men (HET), healthy homosexual men (HOM), men with the lymphadenopathy syndrome (LAS) and those with the acquired immunodeficiency syndrome (AIDS). An asterisk indicates a significant difference from healthy heterosexual subjects ($P<.05$). Values represent mean ± standard error of the mean.

is associated with gastrointestinal ulceration.[26] In AIDS patients, however, disseminated candidiasis has been rare.

Intestinal Parasites

Cryptosporidium

Cryptosporidium muris, a coccidial protozoon, was initially recognized in the gastric glands of mice.[27] Subsequently, the same organism has been reported to infect other animals including calves,[28] turkeys,[29] foals[30] and lambs.[31] *Cryptosporidium* in humans undergoes sexual and asexual stages of development within the mucosa of the small and large intestine. Subsequently, it produces oocysts that are excreted in the stool and that can infect another host.[32]

Cryptosporidium increasingly is being recognized as a pathogen in immunocompetent hosts, especially those with animal contact.[33] This organism is spread by the fecal-oral route. A survey of immunologically normal patients in hospital with gastroenteritis showed that 4.1% excreted *Cryptosporidium* oocysts in their feces.[34] Children had a higher infection rate (7%) than adults (1.6%). In an immunocompetent host, *Cryptosporidium* typically causes a self-limited flu-like illness, with diarrhea as its prominent symptom. Therapy is not required. In contrast, reports of infection with *Cryptosporidium* in patients with humoral and cellular immunodeficiencies and in those undergoing immunosuppressive therapy have documented a chronic and severe diarrheal illness.[35,36] Diarrhea may be accompanied by dehydration, electrolyte imbalance and malnutrition and may require parenteral nutritional and fluid support. Accompanying symptoms have included nausea, vomiting and abdominal pain. In those receiving immunosuppressive therapy, withdrawal of therapy often clears the infection.

Cryptosporidium in patients with AIDS can present as an incapacitating illness with chronic profuse diarrhea and weight loss.[37] The mechanism responsible for diarrhea is not clear, although active secretion in the small bowel has been suggested. Patients may have 6 to 25 liquid stools per day

TABLE 1.—*Abnormalities in Mononuclear Cells in the Intestinal Mucosa of Groups of Homosexual Men*

Homosexual Men With the Lymphadenopathy Syndrome or AIDS
Increased mucosal mononuclear cells
Decreased total mucosal T cells
Decreased mucosal T helper/inducer cells
Decreased helper/suppressor T-cell ratio in the intestinal mucosa and circulation
Homosexual Men With AIDS
Increased proportion of cytotoxic/suppressor T cells in the intestinal mucosa.
Healthy Homosexual Men
Helper/suppressor T-cell ratio normal in the intestinal mucosa but decreased in the circulation.

AIDS = acquired immunodeficiency syndrome

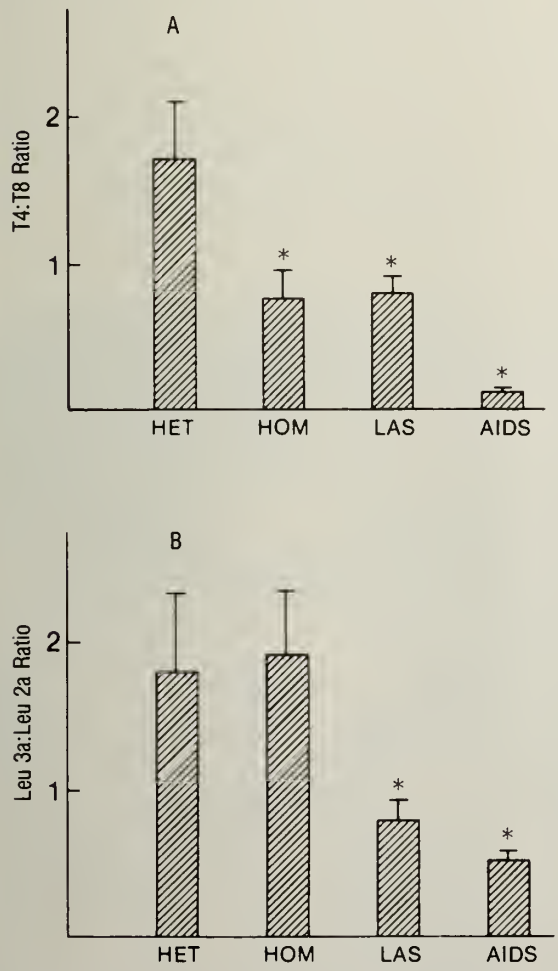

Figure 2.—Helper (T4)-suppressor (T8) T-cell ratios in the intestinal mucosa and circulation of healthy heterosexual men (HET), healthy homosexual men (HOM), men with the lymphadenopathy syndrome (LAS) and those with the acquired immunodeficiency syndrome (AIDS). **A,** OKT 4:OKT 8 ratios in the circulation. **B,** Parallel Leu 3a:Leu 2a ratios in the intestinal mucosa. An asterisk indicates a significant difference from healthy heterosexual men ($P < .05$). Values represent mean ± standard error of the mean.

Figure 3.—A double-contrast barium roentgenogram of the esophagus in a patient with esophageal candidiasis shows diffuse mucosal irregularity and ulceration.

with total stool volumes of 1 to 17 liters. Fluid and electrolyte losses may be accompanied by malabsorption, leading also to severe nutritional and electrolyte abnormalities. Diarrhea can persist for months or until a patient's death due to other complications of AIDS. In some patients with AIDS, infection is asymptomatic, but the organism may be found on the screening of stool specimens.[38] *Cryptosporidium* in AIDS patients has infected mucosal surfaces in the small bowel, colon, gastric mucosa and biliary tract, and patients have been reported to have cholecystitis associated with this organism.[39-41]

The diagnosis of cryptosporidiosis is made by identifying the organism on stool examination using stool-concentration techniques and phase-contrast microscopy.[42] In addition, a modified Ziehl-Neelsen stain for acid-fast bacilli (AFB) will elicit the organism in stool as a 3- to 6-micron densely stained red spherule.[43] More recently, auramine, a fluorescent stain, has been used for detecting *Cryptosporidium* in stool specimens.[44] A small bowel biopsy specimen from a patient with cryptosporidiosis typically shows villous atrophy and crypt hypertrophy together with 2- to 5-micron round organisms that appear to be adherent to the mucosal membrane (Figure 4).[45] In tissue sections the organism is best shown by a modified Kinyoun stain.[46] Electon microscopy of the intestinal mucosa reveals the various life-cycle stages of *Cryptosporidium*, together with a specialized attachment organelle. Such studies suggest that the organism may be located beneath the apical membrane of intestinal epithelial cells.[47] Small bowel radiographs may show thickened and blunted mucosal folds in the proximal small intestine and occasionally a rigid contracted gastric antrum.[48] In some patients, combined stool examination and small bowel biopsy may be necessary for diagnosis.

In general, the results of using antibiotics in the treatment of cryptosporidiosis have been discouraging.[49] Spiramycin, an erythromycin-like drug initially used to treat patients infected with *Toxoplasma gondii*, has in a few reports had limited success when used at a dose of 1 gram three to four times per day for one week. In a study of ten patients, six had complete resolution of diarrhea and three of these had negative follow-up fecal examinations.[50] Another four patients in this study had symptomatic improvement, but the organism did not clear from the feces. A separate study reported that 3 of 13 patients were cured symptomatically and by results of a stool examination after three to four weeks of treatment with spiramycin.[51] In an additional three patients, there was symptomatic improvement but no clearing of the organism from the feces, and discontinuing the therapy in those patients resulted in relapse. The remaining seven patients did not have response to the medication.

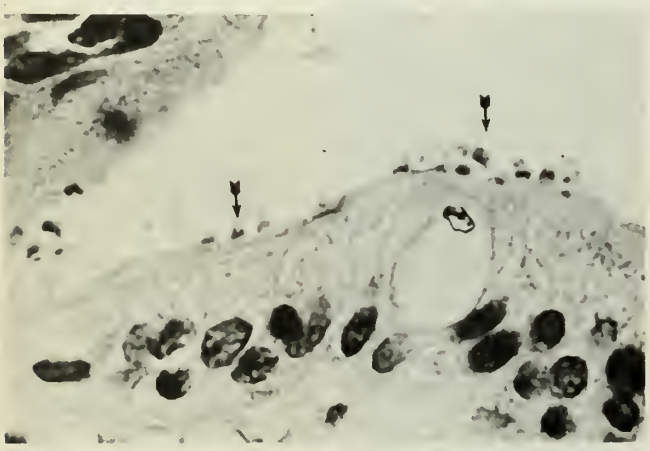

Figure 4.—A biopsy specimen of small bowel mucosa shows cryptosporidia **(arrows)** at the epithelial cell surface (hematoxylin-eosin stain, original magnification × 400; photomicrograph courtesy of J.W.M. Gold, MD).

Isospora belli

Isospora belli is a rare intestinal parasite that is most common in the tropics and has been associated occasionally with intestinal infections among immunocompetent and immunocompromised hosts in the United States.[52] This organism has been identified in a small number of patients with AIDS who have chronic diarrhea and malabsorption, particularly in those from Haiti.[53] Transmission probably occurs by the fecal-oral route. In immunocompetent patients, infection typically presents as a transient illness characterized by diarrhea, weight loss, abdominal pain, anorexia, vomiting and fever.[54] Steatorrhea also may be present. Peripheral eosinophilia has been noted in about 50% of immunocompetent patients infected with *I belli*,[55] and Charcot-Leyden crystals variably have been found on stool examination.

Isospora infects epithelial cells of the small intestine (Figure 5). The organism undergoes asexual and sexual stages of replication, with subsequent production of the characteristic oval or flask-shaped double-walled oocyst.[56] Finding cysts in stool specimens is difficult, even during periods of severe diarrhea or steatorrhea, although identification can be enhanced by using flotation techniques to concentrate the

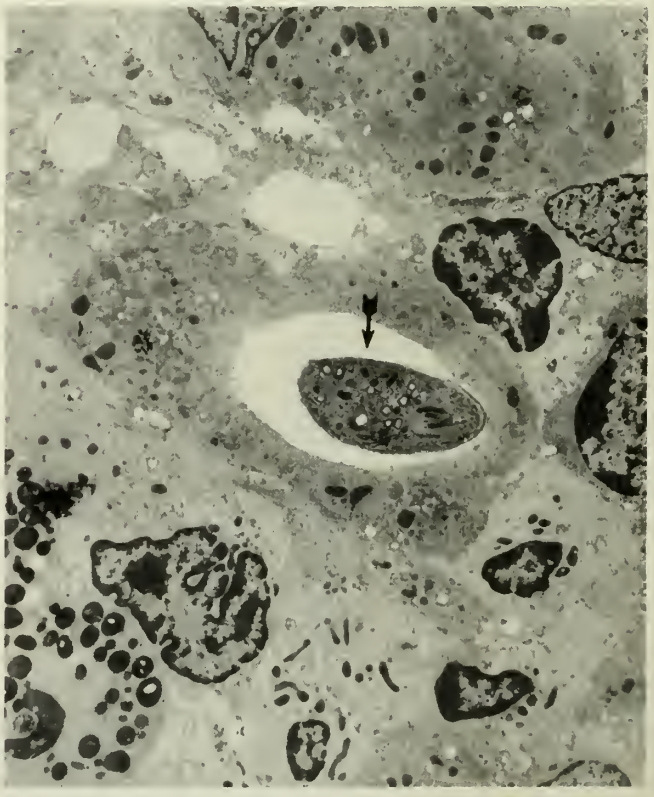

Figure 5.—An electron micrograph shows an *Isospora belli* organism within an intestinal epithelial cell **(arrow)** (uranyl acetate and lead citrate stain, original magnification × 7,000).

cysts.[57(pp1002-1003)] AFB stains also may be helpful for identifying cysts in stool specimens.[58] The diagnosis is more typically made by examining the duodenal contents or a biopsy specimen of small intestinal mucosa.[59] Giemsa staining has been the most useful technique for showing the various stages of *I belli* within the epithelial cells of the small intestinal mucosa. The mucosal architecture usually is altered with villous clubbing or flattening and lymphocytic infiltration of the lamina propria. Radiographic examination of the small bowel may elicit no abnormalities or may show distended small bowel loops and edema of the mucosa.

Infection is self-limited in immunocompetent persons and may last from six weeks to six months. In immunocompromised patients, however, including those with AIDS, symptoms may be prolonged.[60] Various antibiotics such as pyrimethamine and sulfadiazine,[59] trimethoprim-sulfamethoxazole and co-trimoxazole[61] have been tried with some success.

Microsporidia

Microsporidia belong to a phylum of protozoan parasites that includes pathogens for mammals,[62] fish[63] and arthropods.[63] In AIDS patients, the microsporidia found in the intestinal mucosa have differed morphologically from those reported previously in other organs.[64] Microsporidia have typically been found in patients with AIDS who have diarrhea that, after careful examination for enteric pathogens, has been termed idiopathic.[65] These organisms frequently are missed, even on careful examination of intestinal tissue by light microscopy, because of their small size, intracellular location and poor staining with the usual tissue stains. Small intestinal biopsy specimens may show an increase in mucosal macrophages or plasma cells, but not villous atrophy. Electron microscopy is currently the most useful technique for identifying microsporidia in the intestinal mucosa.[66] The organism typically is seen in the apical area of a villus, and approximately 10% of the epithelial cells are invaded. In some persons, an increase in secretory granules within epithelial cells has been recognized. Microsporidia spores are 1 to 2 microns in diameter and have not been identified in the feces of patients. Even though microsporidia are associated with diarrhea, it has not been proved thus far to be the cause of the diarrhea. There is no known effective treatment of infection with this organism.

Bacteria

Mycobacterium avium-intracellulare

Mycobacterium avium-intracellulare is an atypical mycobacterium that is an important pathogen in patients with AIDS.[67] *M avium-intracellulare* is common in the environment. Before the description of AIDS, it was recognized occasionally to cause disseminated infection in patients with proved or suspected immunocompromised states.[68] It was more typically recognized as a pulmonary pathogen in persons with intrinsic lung disease.[69]

In patients with AIDS, *M avium-intracellulare* often is widespread with involvement of the lymph nodes, spleen, liver, bone marrow, intestinal tract, adrenal glands and brain.[70] It typically is spread hematogenously and blood cultures may be positive.[71] Identification, however, may require the use of specialized culture media, such as the Dupont isolator.[72] Typically, once blood cultures are positive, subsequent blood cultures remain positive, suggesting a sustained bacteremia.[73] Diagnosis also can be confirmed by examining bone marrow, liver or lymph node biopsy specimens. Tissue sections may show granulomas, which microscopically consist of a collection of large, round macrophages with pale, somewhat foamy cytoplasm.[74] On Ziehl-Neelsen staining, typical acid-fast bacilli can be seen within the macrophages. A lymph node biopsy specimen often shows lymphocyte depletion together with macrophages containing abundant AFB. Of note, granuloma formation may not be present in AIDS patients due to abnormal macrophage and T-cell function. Acid-fast bacilli should be sought in all tissues in suspected cases.

Gastrointestinal involvement, typically in the small bowel, can result in diarrhea and malabsorption.[75] Upper gastrointestinal tract endoscopy may show small superficial ulcerations of the duodenal mucosa.[76] On biopsy specimens, periodic acid-Schiff-positive, diastase-resistant macrophages may be present throughout the intestinal mucosa, reminiscent of the appearance of Whipple's disease (Figure 6).[76] Acid-fast bacilli can be found in macrophages and free in the lamina propria. By electron microscopy, intact rod-shaped bacilli are seen within the cytoplasm of the macrophages. In contrast, in Whipple's disease, a disease also reported to have T-cell or macrophage abnormalities or both,[77,78] the bacilli within intestinal mucosal macrophages typically show partial dissolution.[79]

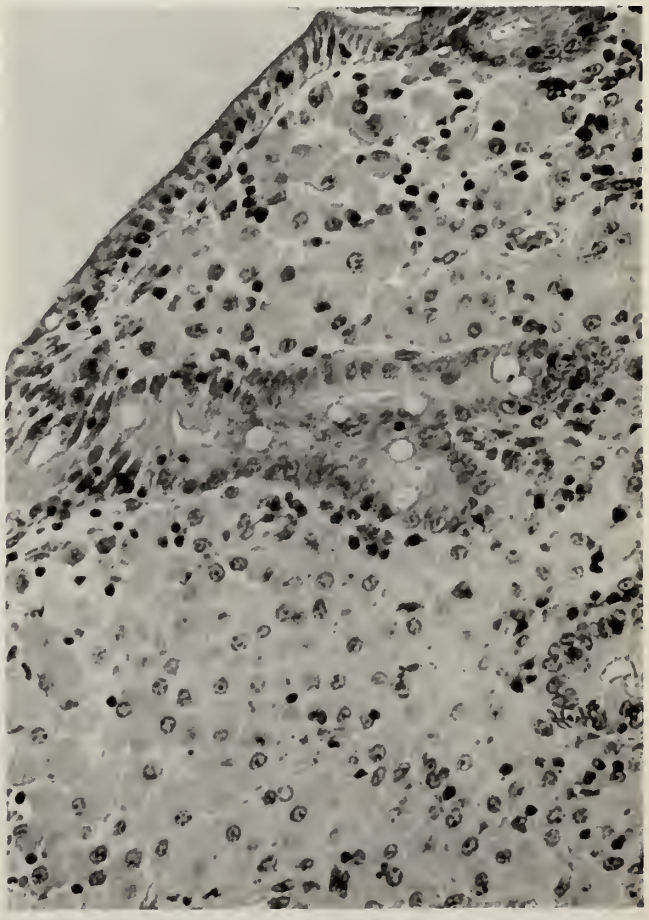

Figure 6.—A small bowel biopsy specimen shows multiple foamy macrophages in the lamina propria of a patient with *Mycobacterium avium-intracellulare* (hematoxylin-eosin stain, original magnification × 400).

Treatment of infection with *M avium-intracellulare* has been difficult. The use of combinations of multiple antituberculous drugs has had disappointing results.[80] Ansamycin and clofazimine have shown some in vitro activity against many isolates of *M avium-intracellulare*, but in vivo experience with these drugs has been limited.

Viruses

Cytomegalovirus

Mounting evidence, including identifying cytomegalovirus (CMV) in specimens from the uterine cervix,[81] urine and semen,[82,83] has suggested sexual transmission of this virus. In one study, significant CMV antibody titers were found in 94% of homosexual men compared with 54% of heterosexual men attending a venereal disease clinic.[84]

Before AIDS was recognized, disseminated CMV infection usually was limited to immunosuppressed patients, especially those who had undergone renal,[85] cardiac[86] or bone marrow transplants.[87] Gastrointestinal involvement was rare and was mainly limited to isolated segments of the intestine, with single or multiple mucosal ulcerations. Complications included bleeding or perforation.[88,89] In some cases, CMV appeared to be a secondary invader of ulcerating lesions of the gastric mucosa.[90]

In patients with AIDS, CMV has been identified at autopsy in the small intestine, colon, liver and pancreas.[91] CMV has been reported in association with either discrete colonic lesions[92] or, more commonly, with patchy diffuse lesions suggestive of inflammatory bowel disease.[93] Most patients have a protracted course of diarrhea, although some may present with severe hemorrhagic colitis or colonic perforation and peritonitis.[94] Esophageal, gastric or duodenal involvement characterized by discrete ulcers or generalized edema and inflammation also may be seen.

Radiographic findings vary depending on the site of infection. On upper gastrointestinal tract barium studies, CMV involvement of the stomach and duodenum may be recognized by edema, nodularity, ulceration and poor distensibility of the mucosa.[95] Small bowel involvement has typically been confined to the duodenum, proximal jejunum and terminal ileum. Colonic involvement may appear on plain films as irregular, thickened, air-filled colon as occasionally seen in patients with acute ulcerative colitis. A barium enema study may show diffuse inflammatory changes with mucosal granularity, superficial erosions, luminal narrowing and absent haustral markings.[96] Some patients may have involvement limited to the terminal ileum or cecum.

Endoscopic findings in AIDS patients with gastrointestinal CMV infection vary substantially. In some, discrete ulcers suggestive of early pseudomembranous colitis are seen.[92] Others have more diffuse inflammatory changes characterized by edema, erythema and mucosal erosion.[93] An endoscopic biopsy of these lesions typically shows mucosal ulceration and an inflammatory infiltrate. Intranuclear inclusion bodies are seen in epithelial and endothelial cells (Figure 7). CMV may induce a vasculitis that affects the submucosal capillaries and arterioles resulting in thrombosis and ischemic damage with subsequent perforation and peritonitis.[97]

Treatment results have been disappointing. CMV, like herpes simplex, is a DNA virus. Nonetheless, treatment of CMV infection with acyclovir has not been effective.[98] However, 9-(1,3-dihydroxy-2-propoxymethyl)guanine, a drug that is structurally similar to acyclovir, has shown efficacy in patients with CMV colitis and retinochoroiditis.[99]

Herpes Simplex Virus

Chronic ulcerating lesions due to herpes simplex virus (HSV) are unusual. Such lesions typically are found in patients receiving immunosuppressive therapy or high-dose corticosteroids,[100,101] those with advanced lymphoproliferative disease[102] or in patients with primary immunodeficiency syndromes.[103]

Herpes simplex proctitis in homosexual men may be associated with perianal involvement.[104] Spread outside the perianal area suggests a compromised immune system and, when chronic, is diagnostic of AIDS.[105] HSV proctitis has clinical features that distinguish it from other infectious causes of acute proctitis.[106] It tends to be limited to the distal 10 cm of the rectal mucosa, and associated inguinal lymphadenopathy may be found. Symptoms of HSV proctitis characteristically include hematochezia, tenesmus and constipation. The anorectal pain, however, typically is more severe than with other forms of proctitis. Other symptoms in men with HSV proctitis include hesitancy of urination, perianal paresthesias, posterior thigh pain and impotence. Involvement of the sacral

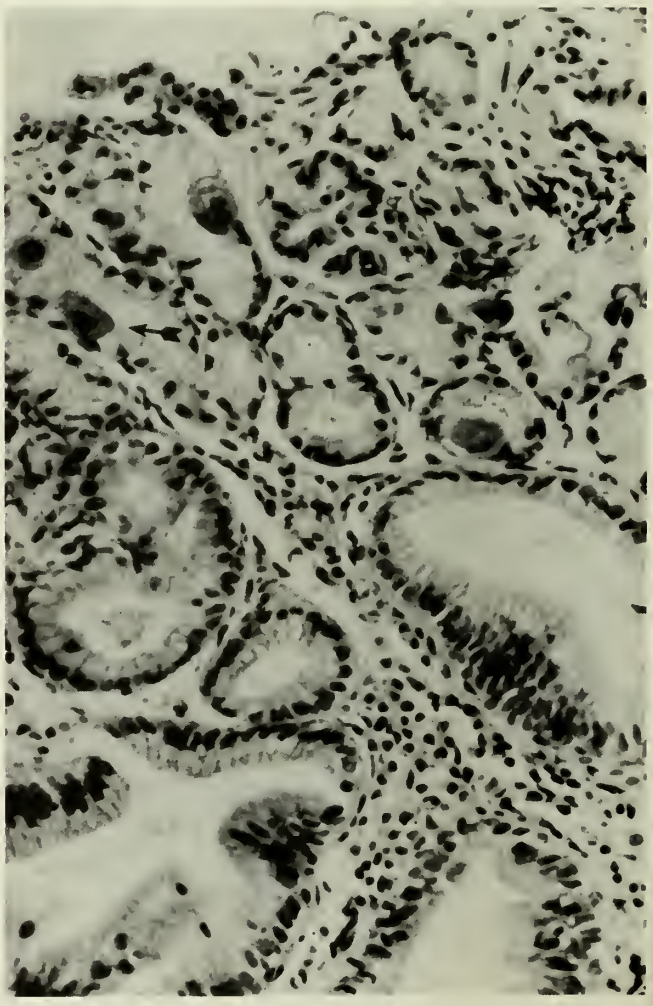

Figure 7.—A specimen of colonic biopsy from a patient with cytomegalovirus colitis shows an intranuclear inclusion **(arrow)** (hematoxylin-eosin stain, original magnification × 400).

autonomic nerve roots is thought to be the cause of many of these symptoms. In the terminal stages of disease, the virus may spread to the spinal cord.

Biopsy specimens of lesions may show inclusion bodies characteristic of herpes simplex virus. Viral cultures are also helpful in establishing the diagnosis, but serologic evidence of HSV infection often is unreliable. These patients usually respond to therapy with antiviral drugs such as acyclovir, but relapse is common.[107]

Kaposi's Sarcoma

Kaposi's sarcoma is a multifocal tumor of the reticuloendothelial system that involves the skin and subsequently the viscera.[108] Classic Kaposi's sarcoma seen in an elderly ethnic population is an indolent disease, typically affecting the extremities, with a mean survival of 8 to 13 years after diagnosis.[109] Visceral involvement is clinically noted in 10% of those with cutaneous disease, although results of autopsy studies suggest visceral involvement in as many as two thirds of affected persons.[110]

A more aggressive lymphadenopathic form of Kaposi's sarcoma has been recognized in young men in equatorial Africa and more recently in young homosexual men with AIDS.[111,112] Approximately 50% of AIDS patients who have cutaneous involvement with Kaposi's sarcoma also have visceral involvement assessed by radiographic and endoscopic studies.[113]

Oropharyngeal involvement is common and this area should be carefully examined in patients at risk for Kaposi's sarcoma.[114] The hard and soft palates are the most commonly affected sites, although lesions of the oral mucosa and gingiva also occur.[115] Oral involvement does not appear to correlate with the presence of Kaposi's sarcoma in other gastrointestinal organs.[116] In patients with AIDS, visceral involvement of the stomach, colon, small bowel, liver and spleen with Kaposi's sarcoma has been found.[117] Typically the lesions are asymptomatic clinically and found at autopsy.[118] Documentation of visceral involvement indicates a worse prognosis in patients with either classic Kaposi's sarcoma or AIDS.[116]

Radiographic evaluation of patients with cutaneous disease often is useful in showing gastrointestinal involvement.[119] Esophageal radiographs have shown polypoid lesions in the midesophagus.[120] The stomach and proximal small bowel are involved more commonly than the distal small bowel or colon.[121] Multiple submucosal defects are typically seen randomly distributed in the stomach, but are more numerous in the antrum. These appear as smoothly contoured polyps ranging from a few millimeters to several centimeters in size. In rare cases lesions have central collections of barium, consistent with the classically described bull's-eye lesion. Other lesions have thickened and irregular mucosal folds. Lesions in the distal small bowel appear nodular, at times with diffuse thickening. Colonic lesions usually appear as distinct nodular submucosal defects. They also may have a skip pattern suggestive of Crohn's disease or present as narrowed nodular rigid lesions typical of adenocarcinoma.

Evaluation of visceral involvement in Kaposi's sarcoma by computed tomography (CT) may show retroperitoneal lymphadenopathy. In patients who also have documented peripheral lymph node involvement, this suggests infiltration with tumor.[122] Adenopathy may vary from large matted collections of lymph nodes with obscuration of surrounding vascular structures, to more discrete and isolated lymphadenopathy. Two cases have been reported of patients with thickening of the posterior rectal wall on computed tomography that was proved histologically to be infiltration with Kaposi's sarcoma.[122]

Endoscopy is more sensitive for detecting gastrointestinal tract involvement of Kaposi's sarcoma than radiography due to its ability to show small flat lesions that may be missed by x-ray film. The usual lesion identified at endoscopy is a discrete, round, nodular lesion that is reddish, purplish or bluish and protrudes into the lumen. Some of these lesions have central umbilication whereas others have superficial ulcerations. Results of endoscopic biopsy usually are normal because of the submucosal nature of the lesions. A histologic diagnosis is based on the presence of bundles of spindle-shaped cells that produce a vascular structure with cleftlike spaces containing erythrocytes or hemosiderin. The surrounding tissue may show infiltration by erythrocytes, lymphocytes and histiocytes. The tumor originates in the submucosa, but may spread through the muscularis to the serosa. Mesenteric lymph node involvement has been noted at operations and at autopsy.

Most Kaposi's sarcoma lesions are clinically asymptomatic. More advanced lesions may result in gastrointestinal tract bleeding and occasionally have been associated with intestinal obstruction, diarrhea and protein-losing enteropathy.[123] One patient was reported to have a periappendiceal abscess due to an obstructing Kaposi's sarcoma tumor in the lumen of the appendix.[119]

Treatment of Kaposi's sarcoma with chemotherapeutic agents has been complicated by the immunosuppression caused by these drugs in already immunocompromised hosts. Patients, however, have shown some tumor regression with both a single agent and combination chemotherapy,[124] and interferon therapy has been useful in reducing tumor size in some patients.[125]

Lymphoma

An increased incidence of B-cell lymphoma has been recognized in patients with AIDS, particularly those with a preceding lymphadenopathy syndrome.[126] These tumors are associated with unusual prodromal manifestations. They often present at an advanced stage and frequently with primary brain or extranodal involvement.[127] Most commonly, these lymphomas involve the central nervous system, although disseminated visceral involvement has been identified in a small number of patients.

In patients who do not have AIDS, 1% to 2% of all primary gastrointestinal malignant disorders occur in the small intestine, and less than 30% of these are lymphomatous in nature.[128-130] The tumors are usually localized in the ileum and often present as a single lesion.

A small number of patients with AIDS have had lymphomas primarily involving the gastrointestinal tract.[131] All patients with primary small bowel lymphoma have preceding generalized lymphadenopathy, but the clinical presentation has varied. For example, one patient presented with a right lower quadrant abdominal mass with a presumptive diagnosis of appendicitis. At laparotomy he had a midileal perforation with peritonitis. On histologic examination there was a

large-cell lymphoma with associated ulceration and peritonitis. A second patient presented with rectal pain, drainage and rectal abscess. Colonoscopy showed involvement of the hepatic flexure and rectum with an ulcerated mass that did not reveal tumor on biopsy. A subsequent laparotomy for small bowel obstruction showed several tumor nodules in the small bowel mesentery. On histologic examination there was a large-cell lymphoma involving the mesenteric lymph nodes and adipose tissue. A third patient presented with abdominal pain, weight loss and constipation. A small bowel series showed a mass in the jejunum. Laparotomy and subsequent resection showed a circumferential, transmural large-cell lymphoma. At least one case of primary large-cell lymphoma of the liver has been reported.[132] Several other cases have been reported of patients with oral lesions.[126]

Due to the rarity of such tumors, the diagnosis usually is not made until late in the clinical course. Treatment of these patients with chemotherapy is complicated because of their underlying immune deficiency and the risk of opportunistic infection. These tumors may be palliated by resective therapy, however.

Idiopathic Diarrhea

Diarrhea, alone or accompanied by generalized lymphadenopathy, fever and weight loss, may precede a diagnosis of AIDS by months and can remain a chronic debilitative problem throughout the course of disease.[133] Often in these patients and in patients with AIDS there is no clear cause for the diarrhea despite aggressive measures to identify a pathogen. Before being classified as idiopathic, evaluation of the diarrhea in such persons should include screening of a stool specimen for enteric pathogens, examination of specimens of small bowel biopsy and aspirates, endoscopic evaluation of the colonic mucosa and barium contrast studies.

Among 72 AIDS patients referred for diarrhea in one study, no identifiable cause could be found in 20 by stool screening for pathogens.[134] All 20 patients had positive D-xylose tests and evidence of fat malabsorption. In 5 of the 20, histologic examination of a duodenal biopsy specimen showed a dense histiocytic infiltration containing AFB-positive organisms that suggested intestinal involvement with *M avium-intracellulare*. Chronic nonspecific inflammation characterized by plasma cell and lymphocytic infiltrates with normal villous architecture was found in 13 of the 20. Two patients had normal-appearing intestinal mucosa. Another study has documented significant weight loss and a decrease in hemoglobin, iron-binding capacity, albumin levels and mid-arm circumference in patients with AIDS who have chronic diarrhea compared with homosexual controls.[17] D-Xylose absorption was abnormal in all, and fat malabsorption was noted in 8 of 11 patients with AIDS. Jejunal biopsy specimens from several of the AIDS patients with diarrhea revealed partial villous atrophy, crypt hyperplasia and an increase in intraepithelial lymphocytes. Rectal biopsy specimens showed focal epithelial cell degeneration, viral inclusions and mast cells located near the base of the rectal crypts.

The cause of diarrhea in many patients with AIDS has defied diagnostic techniques. One may speculate that unidentified viral infections are responsible. In one study, electron microscopy of postmortem intestinal mucosal specimens showed small spherical viruslike particles within epithelial cells of two of six patients with AIDS.[135] In one patient, they were localized to the ileal mucosa and in the other to the rectal mucosa. The significance of those findings, however, or of HIV infection in the gut with respect to diarrhea is unclear at present.

Enteric Bacteremias

Salmonella

Salmonella can be sexually transmitted in homosexual men.[136] In patients with AIDS, *Salmonella* bacteremias can be recurrent despite prolonged antibiotic therapy,[137-140] perhaps reflecting an abnormality in macrophage function. Most cases have involved *Salmonella typhimurium*, and cases often have occurred in patients from Zaire or Haiti, possibly reflecting a higher exposure and carrier rate in those populations. Antibiotics such as ampicillin and chloramphenicol have been used for treatment. Long-term suppressive therapy with oral administration of antibiotics has been suggested, although there is some concern over inducing antibiotic resistance with such prolonged therapy.

Campylobacter

Campylobacter species, particularly *Campylobacter jejuni*, are well recognized as a cause of enterocolitis.[141] These organisms are transmitted by the ingestion of contaminated food, milk and water or by close contact with infected humans or other animals.[142-144] In addition, three groups of *Campylobacter*-like organisms can be distinguished by their growth pattern, temperature sensitivity and biochemical profile.[145]

Previous studies failed to show an increased incidence of infection with *C jejuni* in homosexual men.[146,147] A recent study of homosexual men attending a venereal disease clinic, however, found *C jejuni* in 10/158 (6.3%) of those persons with intestinal symptoms and in 2/75 (2.7%) of those without intestinal symptoms.[148] Other *Campylobacter*-like organisms were identified in 26/158 (16%) of symptomatic homosexual men and in 6/75 (8%) of asymptomatic homosexual men, but in none of 150 asymptomatic heterosexuals.[148] Infection was more frequent in patients with a history of oral-anal contact.

Presenting symptoms in *Campylobacter* infection may include diarrhea, abdominal cramps, tenesmus and hematochezia. Endoscopic evaluation of the rectal mucosa is characterized by focal and diffuse friability and ulceration. A stool specimen typically shows fecal leukocytes. Isolation and identification of these organisms requires specialized culture media.

A recent study described the cases of two patients with bacteremia caused by *Campylobacter*-like organisms.[149] Typically the patients presented with prolonged fever, and one was found to have a compromised immune system. Neither of these patients had gastrointestinal tract symptoms. Although cultures of stool specimens were not done, the organisms were identified using special blood culture media. Treatment with antibiotics, including rifampin and tetracycline, led to clearing of the bacteremia.

Liver Disease

There is no pathognomonic lesion of the liver in cases of AIDS. Patients with AIDS, however, have one or more risk factors for the development of liver disease. These include a past history of hepatitis or intravenous drug abuse, dissemi-

nated infection, neoplastic disease and treatment with hepatotoxic medications. Hepatomegaly, elevation of serum aminotransferase levels and mild increases in alkaline phosphatase levels are commonly noted in patients with AIDS.[150] A normal bilirubin and elevated alkaline phosphatase values may be seen in those with opportunistic infections or tumors involving the hepatic parenchyma. On histologic examination of hepatic tissue at autopsy, congestion, fatty change, inflammatory processes or tumor is typically found.[150]

Opportunistic infections often involve the liver in patients with AIDS. Hepatic involvement is reported in 5% to 44% of patients with CMV infection. CMV on a liver biopsy specimen is characterized typically by intranuclear and intracytoplasmic inclusions in Kupffer's cells, endothelial cells and hepatocytes, particularly in the sinusoidal areas.[150,151] In one series of patients with disseminated infection with *M avium-intracellulare*, 57% had hepatic involvement.[150] Involvement may be diffuse and characterized by poorly formed granuloma containing foamy histiocytic cells and a lack of other inflammatory cells.[150] Often there is no granuloma, however, and the organism is recognized only on AFB stain or culture. Several AIDS patients have had hepatic involvement with disseminated *Cryptococcus neoformans*. The organism was found in the sinusoids and accompanied by minimal inflammatory response.[150]

Viral hepatitis is common in homosexual men, although the prevalence of seropositivity for hepatitis B in homosexual men with AIDS does not appear to be higher than among other groups of homosexual men.[152] At autopsy of AIDS patients with hepatitis B, there has been a relative paucity of evidence of chronic active hepatitis, as assessed by histology.[151] This may reflect an impaired immune system and an inflammatory response.

Histologic studies in children with AIDS and hepatitis have shown lobular and portal lymphocytic infiltrates, hepatocellular and bile duct damage, sinusoidal cell hyperplasia and endothelialitis suggestive of chronic active hepatitis.[153] T cells of the T8 suppressor/cytotoxic subset predominated in the lymphocytic infiltration. By electron microscopy, vesicular rosettes and tubuloreticular structures were found. The children lacked hepatitis B surface antigen and antibody, yet all were positive for Epstein-Barr virus antibody, leading to the suggestion that such lesions may be caused by Epstein-Barr virus or HIV.

Kaposi's sarcoma involves the liver in 14% of cases.[151] Typically these patients also have involvement of the skin and other abdominal organs. Spindle cell proliferation is frequently seen in the capsule of the liver and appears to extend into the liver parenchyma in a multifocal fashion with a predilection for the portal tracts.[150] Elevated alkaline phosphatase levels have been noted in every case. Finally, primary hepatic involvement with lymphoma has been reported in at least one patient with AIDS.[154]

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Clinicopathologic Conference

Dementia and Ataxia in a Patient With AIDS

Discussants
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HARRY V. VINTERS, MD:* This 29-year-old homosexual man had a history of multiple sexual partners, one of whom had died of acquired immunodeficiency syndrome (AIDS) and the clinical diagnosis of AIDS encephalopathy—that is, progressive dementia terminating in coma. His medical history included an episode of hepatitis and treatment at a drug rehabilitation center two years previously. The patient was in his usual state of good health until about 18 months before he died, when he noted white spots on his tongue; biopsy specimens were taken and showed hairy leukoplakia. At about the same time, he noted fevers and sweats, and, based on abnormal helper:suppressor cell ratios in his peripheral blood, the diagnosis of AIDS-related complex was made (November 1984). He was treated at UCLA Medical Center (August 1985) for shortness of breath caused by *Pneumocystis carinii* pneumonia. Thereafter, he noted persistent fevers. Beginning six to seven months before his death, the patient noted decreased mental function, and this gradually progressed to severe dementia and cerebellar ataxia. He was incapable of walking without assistance for the final six months of his life. Four months before he died, he was admitted to hospital for dyspnea not obviously caused by *Pneumocystis* infection. A computed tomographic (CT) scan of the head showed mild cerebral cortical atrophy.

On physical examination in the outpatient clinic three months before death, he appeared ill and wasted and had profound dementia. His blood pressure was 114/90 mm of mercury and heart rate 84 per minute. No funduscopic abnormalities were noted. The oropharynx showed a yeast infection. A large external nasal lesion consistent with Kaposi's sarcoma was present. Coarse rhonchi were detected throughout both lung fields. There was no peripheral edema, organomegaly or lymphadenopathy. On neurologic assessment he had, in addition to dementia, diffuse hyperreflexia with pronounced clonus of the right arm and leg. Diminished motor strength was noted in all flexor muscles, but extension was normal. He had positive palmomental and glabellar reflexes. Detailed sensory testing could not be carried out. For the remaining weeks, he was cared for by friends at home, where he died in June 1986. His mentation was said to show progressive decline over that time interval.

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GREGORY L. CLARK, PhD, MD:* In summary, we are presented with a 29-year-old homosexual man with documented AIDS manifested by the opportunistic infection *P carinii* and Kaposi's sarcoma. He also suffered neurologic complications including severe dementia, cerebellar ataxia, peripheral neuropathy and diffuse weakness in joint flexors. A CT scan done about four months before death showed only mild cerebral cortical atrophy.

For the purposes of this discussion, I shall assume that the dementia referred to in the case presentation is that of persisting cognitive impairment in the absence of significant toxic-metabolic disturbance.

The differential diagnosis of central neurologic complications in a patient with AIDS is quite long, but encompasses viral syndromes, nonviral infections, neoplasms and, less frequently, stroke.[1] Viral syndromes include the recently defined AIDS-dementia complex,[2,3] aseptic meningitis, herpes simplex encephalitis, progressive multifocal leukoencephalopathy, varicella zoster encephalitis and viral myelitis. Nonviral infections include toxoplasmosis, cryptococcosis, candidiasis, aspergillosis, coccidioidomycosis, infection by atypical mycobacteria, tuberculosis and bacterial infections. Neoplasms involving the central nervous system (CNS) include primary lymphoma, systemic lymphoma with brain involvement and Kaposi's sarcoma.

In this case, we can narrow the differential diagnosis by considering that the CT scan showed no focal lesions but only mild cortical atrophy. Progressive multifocal leukoencephalopathy typically presents with characteristic low-density lesions on CT. Toxoplasmosis almost invariably presents with one or more ring-enhancing lesions. In rare instances, however, there have been cases of documented toxoplasmosis with a normal CT scan.[4] In eight recently reported cases of

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(Clark GL, Vinters HV: Dementia and ataxia in a patient with AIDS [Clinicopathologic Conference]. West J Med 1987 Jan; 146:68-72)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
HIV = human immunodeficiency virus

primary CNS lymphoma,[1] the CT scans were normal in three cases, there was homogeneous enhancement in one and there were hypodense areas with peripheral enhancement in four. Metastatic Kaposi's sarcoma to the brain is extremely rare, but a focal lesion was seen in one patient in whom a scan was done.[5] Fungal infections might be expected to present with nonfocal CT findings. CT scans of AIDS patients with cryptococcal infection may show cerebral atrophy or hydrocephalus or may be entirely normal.[1] Information regarding the CT presentation of the remaining fungal infections in AIDS patients is unavailable. CNS tuberculosis could be expected to present with basal enhancement on the CT scan.

The presentation of herpes simplex encephalitis in patients with AIDS has been shown to follow a spectrum ranging from subacute encephalitis with a normal CT scan to a hemorrhagic necrotizing encephalitis. Finally, the so-called AIDS-dementia complex, felt by some to reflect direct cerebral infection by the human immunodeficiency virus (HIV),[2,3] often presents with cortical atrophy, but white matter attenuation is noted in some patients, and in one case a periventricular white matter lesion was seen.[2]

Thus, a CT scan is not helpful in absolutely excluding many causes, and we are additionally hampered by the lack of a cerebrospinal fluid (CSF) examination, which in the absence of a specific focal lesion on CT would help to exclude a number of possibilities. We can say, however, that disorders such as toxoplasmosis, progressive multifocal leukoencephalopathy, typical or atypical mycobacterial infection, CNS lymphoma and metastatic Kaposi's are quite unlikely, based on CT findings alone.

Because there is no history of meningeal signs such as stiff neck, headache or seizures, one might also exclude meningeal infections such as atypical aseptic meningitis, fungal infections and tuberculous as well as atypical tuberculous infections. It is important to recall, however, that there are documented examples of cryptococcal meningitis in AIDS patients presenting with normal neurologic findings and headache as the only neurologic complaint.[1] With the information at hand, an underlying fungal infection cannot be totally excluded.

We are left, then, with the likely diagnosis of a viral syndrome. Varicella zoster encephalitis in AIDS patients has presented as intractable seizures in a patient recovering from a cryptococcal infection at a time when no evidence of active cryptococcosis could be determined.[1] A patient has also presented with multifocal demyelination,[6] but I will exclude this possibility. Another disorder that encompasses progressive dementia with accompanying motor and behavioral dysfunction has been variously called subacute encephalitis, subacute encephalopathy or, more recently, AIDS-dementia complex.[2,3] The dementia is characterized early on by impaired memory and concentration with psychomotor slowing. Early motor deficits include ataxia, leg weakness, tremor and loss of fine motor coordination. Behavioral disturbances usually include apathy and withdrawal, but may include psychosis. The disease ultimately leaves a patient with severe dementia, mutism, incontinence, paraplegia and occasionally myoclonus. The findings of a CSF analysis are generally nonspecific, and, as noted before, the most common CT finding is cortical atrophy.

As defined by Navia and co-workers,[2,3] the syndrome specifically excludes other conditions such as lymphoma, toxoplasmosis and the like as a cause, but these conditions may coexist. Brain cultures in patients with subacute encephalitis have yielded *Mycobacterium avium-intracellulare,* cytomegalovirus (CMV) and herpes simplex and combinations of the above. It has been suggested that subacute encephalitis or the AIDS-dementia complex is due to CMV infection of the central nervous system.[7] A recent study, however, did not support this conclusion.[2,3] Rather, based on clinicopathologic data, these authors agree that CMV was occasionally an associated infection, while the underlying cause was probably direct brain infection by the AIDS retrovirus or human immunodeficiency virus.

In this case, it would appear that within the limited framework of the signs, symptoms and clinical course described, the patient's condition would best fit the diagnosis of AIDS dementia complex.

Dr Vinters: Autopsy (permission obtained by efforts of R. Mitsuyasu, MD, Division of Hematology-Oncology, UCLA), carried out within 12 hours of death, was restricted to the brain, which weighed 1,170 grams and externally showed no abnormality of the leptomeninges, parenchyma or vasculature. Coronal slices (1 cm) of the fixed cerebral hemispheres similarly showed no abnormality apart from a patchy, ill-demarcated area of grey discoloration in the white matter superior and lateral to the left amygdaloid nucleus, minimal thinning of the corpus callosum and slight enlargement of the lateral ventricles. Horizontal sections of the brain stem and parasagittal sections of cerebellum showed no abnormalities aside from minimal splaying apart of folia, a change restricted to the anterior-superior cerebellar vermis.

Despite the normal appearance of the brain by gross inspection, numerous abnormalities were found on histologic sections. A patchy lymphohistiocytic infiltrate, without microorganisms, was present in the leptomeninges. Throughout the cerebral cortex, there were scattered inflammatory foci consisting primarily of activated microglia—changes usually described (in AIDS patients) by the term microglial nodule encephalitis.[8,9] These focal inflammatory aggregates were especially prominent in the subpial regions (Figure 1) and (less often) deep to the ependyma—that is, they were near the surfaces bathed by CSF. Within these foci but more commonly separate from them and distributed randomly throughout the brain were multinucleate giant cells containing foamy or finely granular cytoplasm (Figure 2). These cells are thought to be a manifestation of direct invasion of the brain by the virus that causes AIDS.[3,10-13] The giant cells were particularly prominent around the adventitia of small blood vessels (Figure 2). (Ultrastructural examination of both cerebrum and cerebellum from this patient has thus far failed to show typical HIV particles within these cells.) Foci of necrotizing encephalitis apparently caused by CMV were seen in several areas, but were especially prominent at the floor of the fourth ventricle in the medulla oblongata (Figure

3) and in the corpus callosum, where typical nuclear and cytoplasmic inclusions of CMV were detected within poorly demarcated foci of demyelination. Many cells bearing typical CMV inclusions in the medulla were also stained with a peroxidase-antiperoxidase procedure for glial fibrillary acidic protein (Figure 4), suggesting that they were of astrocyte origin or reactive ependymal cells[14] previously infected by CMV. Areas of calcified necrotizing leukoencephalopathy were noted in both internal capsules and in the medullary white matter of the right cerebellar hemisphere. These regions showed disruption of axons with neuroaxonal spheroids, lipid-laden macrophages, granular calcification and intense reactive gliosis (Figure 5). There was resultant secondary degeneration of the corticospinal tracts bilaterally. Even in areas not affected by necrotizing leukoencephalopathy, there was intense reactive gliosis with numerous gemistocytic astrocytes within the white matter of the centrum semiovale (Figure 6). Within the cerebellum, in addition to areas of cortical CMV encephalitis (Figure 7), there was patchy but focally pronounced loss of Purkinje's cells with reactive Bergmann's gliosis (Figure 8). In a small segment of cervical spinal cord, vacuolar degeneration of the dorsal columns and corticospinal tracts was seen. Though this showed some similarity to the vacuolar myelopathy described in some AIDS patients,[15,16] the corticospinal tract change might be due to the more proximal capsular leukoencephalopathy, while the dorsal column degeneration may reflect Wallerian degeneration due to disease in the dorsal roots or dorsal root ganglia (these could not be examined because of restrictions on the autopsy).

This case illustrates several important and somewhat controversial issues in understanding the neurologic and neuro-

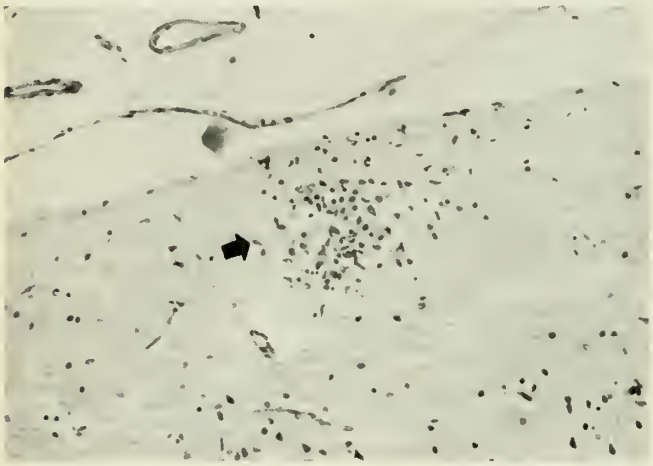

Figure 1.—A section of cingulate gyrus shows an inflammatory (microglial) nodule **(arrow)** in the subpial region (hematoxylin and eosin stain, original magnification × 195).

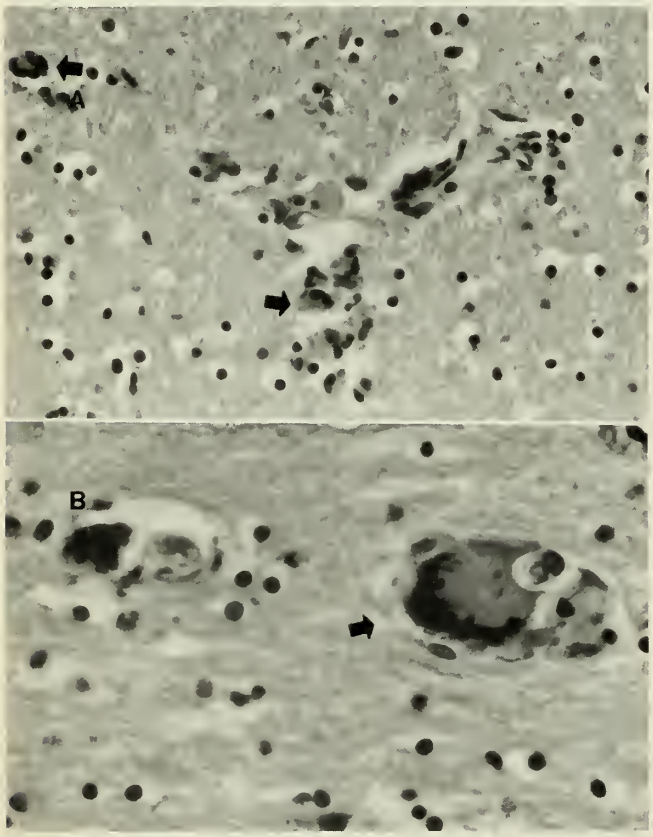

Figure 2.—Multinucleate giant cells **(arrows)** in subcortical white matter of the left frontal lobe **(A)** and in diencephalon **(B)** adjacent to a focus of leukoencephalopathy in the internal capsule (not visible). Giant cells tend to be perivascular and have either little cytoplasm **(A)** or granular/foamy cytoplasm with eccentric nuclei **(B)** (both hematoxylin and eosin stain, **A** original magnification × 500, **B** original magnification × 790).

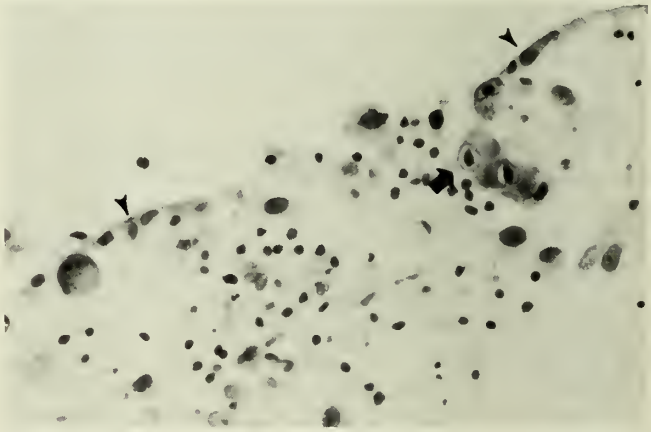

Figure 3.—Cytomegalovirus encephalitis disrupts ependyma **(arrowheads)** of fourth ventricle in medulla. Note typical intranuclear **(arrow)** and cytoplasmic inclusions in ependymal and subependymal cells (hematoxylin and eosin stain, original magnification × 500).

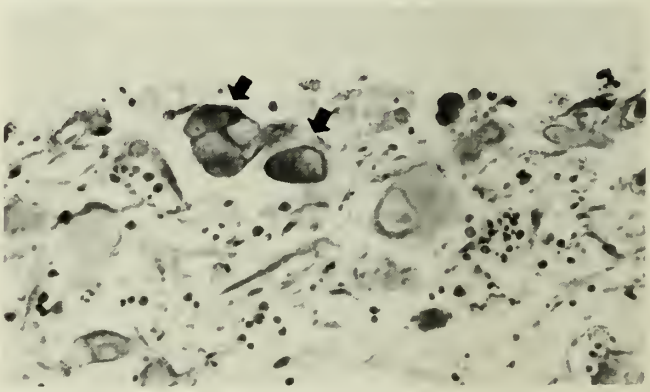

Figure 4.—Subependymal cytomegalovirus inclusion-bearing cells in medulla **(arrows)** show cytoplasmic glial fibrillary acidic protein (GFAP) (peroxidase-antiperoxidase procedure for GFAP, original magnification × 500).

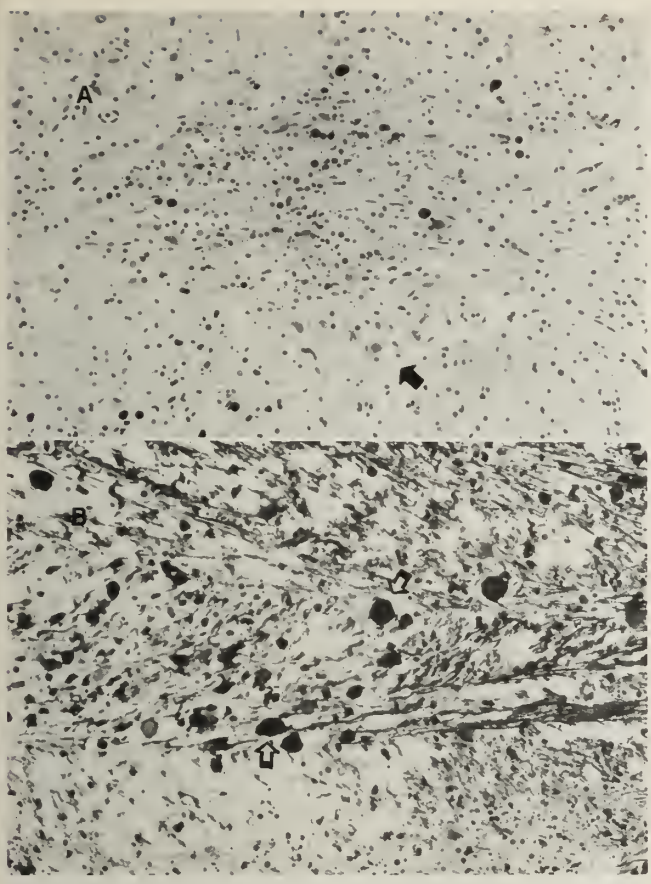

Figure 5.—Necrotizing leukoencephalopathy in right internal capsule shows vacuolation, granular calcification and gliosis **(A)**. Arrow points to gemistocytic astrocytes. Evidence of axonal disruption is seen, with prominent neuroaxonal spheroids **(arrows, B)** (**A** hematoxylin and eosin stain, original magnification ×195; **B** Bielschowsky stain, original magnification ×195).

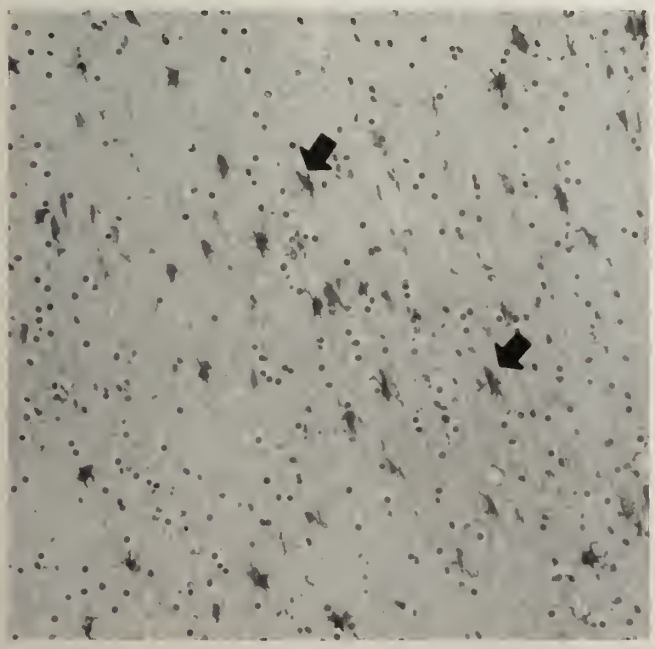

Figure 6.—Left frontal white matter shows reactive hypertrophic gliosis, with prominent astrocytes **(arrows)** (peroxidase-antiperoxidase stain for glial fibrillary acidic protein, original magnification ×195).

pathologic complications of AIDS, particularly AIDS dementia or encephalopathy. The findings in the brain are most consistent with those described by Kleihues and associates[17] in two patients with AIDS, named progressive diffuse leu-

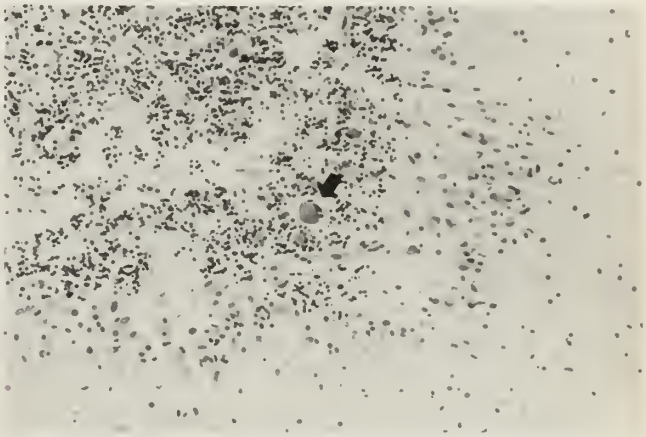

Figure 7.—Focus of cytomegalovirus (CMV) encephalitis in cerebellar vermis. Note severe Purkinje's cell loss and a typical CMV inclusion **(arrow)** (hematoxylin and eosin stain, original magnification ×195).

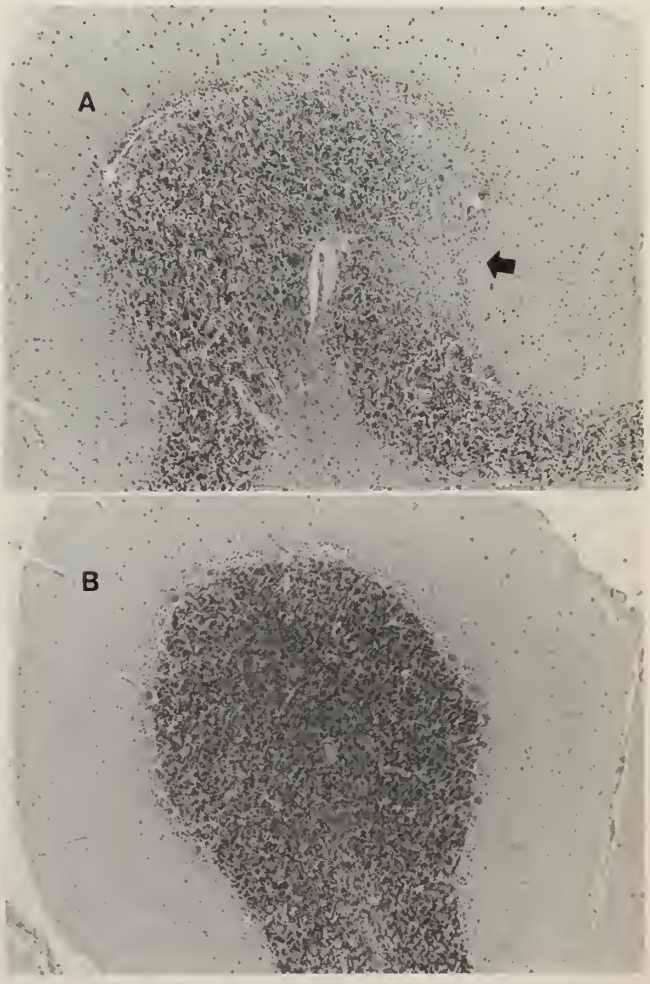

Figure 8.—Cerebellar folia (vermis) from this patient **(A)** and a 52-year-old AIDS patient without ataxia (**B**, control). Note comparatively severe loss of Purkinje's cells and Bergmann's gliosis **(arrow)** in **A** (hematoxylin and eosin stain, both original magnification ×75).

koencephalopathy—that is, leukoencephalopathy more severe in the deep (cerebral and cerebellar) than the subcortical white matter with Wallerian degeneration of long tracts distally, combined with the presence of scattered perivascular giant cells. The latter, as already stated, have been implicated by several investigators as a morphologic hallmark of direct brain infection by HIV. The giant cells have staining features that suggest they are macrophages rather than neuroectodermal cells, but it is unknown whether they originate from the blood or the brain. Several reports now provide evidence that the virus that causes AIDS is to be found in the central nervous system and CSF of patients with neurologic syndromes.[18-22] In rare instances, particles with the ultrastructural appearance of HIV have been seen in the cytoplasm of the previously described giant cells.[10] A recent abstract claims that evidence of HIV infection is found in macrophages, multinucleate cells, astrocytes and basal ganglion neurons of AIDS patients with the AIDS-dementia complex.[23] Kleihues and colleagues felt that the diffuse leukoencephalopathy either was directly related to brain infection by HIV or represented an unusual variant of progressive multifocal leukoencephalopathy caused by papovavirus infection, for which immunohistochemical evidence was presented, though the histologic appearance in both of their cases and in this patient was highly atypical for progressive multifocal leukoencephalopathy.[17] Indeed, lesions of various white matter tracts are common in the brains of a high proportion of patients with AIDS.[9,24-26]

This case is further complicated by the presence of multifocal CMV encephalitis. Areas of the white matter in which CMV was identified frequently showed demyelination of adjacent tracts (such as in the corpus callosum). Others have reported on the association between CMV infection of the nervous system in cases of AIDS and demyelination.[27] Many of the foci of most severe leukoencephalopathy in our patient, however, were clearly remote from zones in which CMV inclusions could be found.

A further intriguing point about this patient is that foci of CMV infection and microglial nodule encephalitis in general were frequently adjacent to surfaces bathed by CSF; for instance, note the severe CMV encephalitis at the base of the fourth ventricle and the numerous subpial microglial nodules. The respective etiologic agents may thus have entered the brain through the blood-CSF barrier (choroid plexus epithelium) rather than crossing the blood-brain barrier, as one might normally expect. CMV infection of the brain in AIDS patients has been shown, by in situ hybridization and immunocytochemical techniques, to seed the ependyma and to spread from there ventriculofugally into the brain parenchyma.[28] The study by Wiley and associates also showed CMV inclusions within cells positive for glial fibrillary acidic protein, which we have confirmed.

Thus the patient's dementia was caused by a combination of diffuse severe leukoencephalopathy, CMV encephalitis and (probable) HIV infection of the brain. Ataxia was the result of CMV encephalitis affecting the cerebellum, leukoencephalopathy affecting the cerebellar white matter and patchy but focally severe loss of Purkinje's cells, most notable in the vermis. The loss of Purkinje's cells may represent yet another direct effect of HIV on the nervous system, though it has not been described in other large series of patients.[1,9,29] Furthermore, it may be attributed to the anoxic-ischemic episodes that this patient almost certainly experienced preterminally.

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Medical Staff Conference

Diet and Cancer—Should We Change What We Eat?

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Our speaker for this conference is Dr Sue Desmond. A graduate of the University of Nevada School of Medicine, she is completing her house-staff training on the medical service at the University of California, San Francisco, serving during this past year as an outstanding Chief Resident at Moffitt Hospital. Her future plans include fellowship training in hematology and oncology. She has chosen a particularly provocative title to discuss, "Diet and Cancer—Should We Change What We Eat?"*

SUSAN DESMOND, MD:† In the May 8, 1986, issue of *The New England Journal of Medicine*, an article entitled "Progress Against Cancer?" attempted to address the overall progress against this disease during the years 1950 to 1982.[1] In 1962 a total of 278,562 Americans died of cancer, a figure that increased by 56% to 433,795 American deaths from cancer in 1982. Even when adjusted for population growth and aging, this figure represents an increase of 8.7%. Incidence rates of all cancers are up in both white women and white men, a fact that suggests a failure to control new cases of cancer. Mortality data are especially striking for increases in deaths from lung cancer, a clear-cut environmentally associated tumor. There has been an apparent increase in mortality from breast cancer among white and nonwhite women since 1950, and mortality from cancer of the prostate in men has not changed appreciably. Mortality from stomach cancer has decreased due to decreases in incidence, and colon cancer has also declined in mortality. The authors' interpretation of these data is that "large monetary expenditures have led to increases in our understanding of cancer, but not to decreases in incidence or mortality."[1] Their conclusion is that a refocusing of our efforts from treatment to prevention is in order.

Cancer and the Environment

It has been estimated that as many as 80% to 90% of all human cancers are attributable to environmental influences and are therefore preventable.[2] This statement is based on the assumption that the lowest rate for each type of malignancy identified in worldwide surveys represents the "natural incidence" of the disease and that environmental factors contribute to the higher rates found elsewhere. For example, the United States has an overall incidence rate of cancer in men approximately 90% higher than that in Honduras, which has the lowest international incidence. The excess deaths could result from environmental factors specific to the United States. There are problems with interpreting data such as these, however, with a large number of "confounding variables," probably the most important being the age structure of the various populations and the completeness with which the causes of death are determined and reported. In the example cited, Honduran men had a 1974 life expectancy of 52 years versus 68 years for American men, an especially important confounding variable because 80% or more of cancer deaths in the United States occur after the age of 55.

Even more striking than international differences in overall cancer rates are those found in site-specific categories in which, for commonly affected sites, tenfold to thirtyfold differences are seen. For example, if one compares the cancer incidence in Bulawayo, Zimbabwe (formerly Rhodesia), and Geneva, Switzerland, liver cancer rates are higher in both men and women in Bulawayo, whereas the rates in Geneva for colon and breast cancer far exceed the Bulawayo rates. In fact, female breast cancer rates in Geneva are five times greater than those seen in Bulawayo. Such pronounced international variations in site-specific cancer rates contain important clues for understanding the etiology of human cancer.[3]

In the past, country-to-country variations in cancer incidence were often attributed to racial or genetic factors. Today most authors agree that these factors account for only a small minority of cancers, with genetic factors directly responsible for no more than 2% of all human cancers. In recent years, the results of studies of migrant populations have severely undermined the concept of racially or genetically based carcinogenesis. Migrant populations basically exchange one environment and its carcinogenic risks for another and its risks.

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(Desmond S: Diet and cancer—Should we change what we eat?—Medical Staff Conference, University of California, San Francisco. West J Med 1987 Jan; 146:73-78)

Because the genetic endowment remains the same in both environments, any large variations from cancer rates in the country of origin are best explained in terms of differences in environmental exposure. Almost all migrant studies have had the same findings: cancer patterns in migrants tend to approximate those in the adopted country and differ from the country of origin.

Cigarette smoking is the best identified environmental factor associated with cancer; other carcinogenic agents include radiation and chemicals (usually occupational exposures) and viruses (a general exposure). With the exception of smoking and occupational hazards, nutrition is probably the most important environmental risk.

In 1984 the American Cancer Society published a list of seven dietary recommendations for avoiding cancer (Table 1). These include both avoiding certain foods, such as fats, and including other foods in the diet, such as cruciferous vegetables.[4]

Obesity and Cancer

The observation that one should avoid obesity to decrease cancer risk comes from both experimental and epidemiologic evidence. It has long been known that laboratory animals fed a low-caloric diet showed a decrease in chemically induced tumors, but that high-caloric diets often were high in fats, so that the effects of calories were difficult to separate from those of fats.[5] When mice are given gold thioglucose, however, which induces obesity via a specific hypothalamic lesion, there is a higher incidence of mammary tumors, so obesity itself may increase tumor formation.[6]

The American Cancer Society did a long-term prospective study over the period 1959 to 1972, drawing 750,000 men and women from the general population.[7] The lowest mortality rates were found in those close to average weight and those 10% to 20% below average weight. Mortality among men and women 30% to 40% heavier than average weight was nearly 50% higher than those of average weight. Excess cancer mortality in obese persons was seen mainly in women, who had more cancers of the gallbladder, breast, cervix, endometrium and ovaries.

Dietary Carcinogens

One very noticeable feature of the American Cancer Society's recommendations is a lack of great emphasis on "carcinogens" in the diet. In fact, only with their final recommendation to decrease the intake of smoked and cured foods (because of their links to gastric and esophageal cancer) is this concept addressed. Contrary to what was thought 20 to 30 years ago, food additives and contaminants have not, with the exception of aflatoxin, proved very important in human cancers. Since the early 1970s there has been a shift in emphasis to general food types in the diet and how they affect our cancer risk.

Advances in analytic technology, especially the Ames test, have disclosed that in experimental systems an astonishing variety of compounds occurring naturally in the diet are carcinogenic or mutagenic.[8] Such commonly consumed foodstuffs as celery, rhubarb, cocoa powder, tea, mustard, lettuce and spinach contain potential mutagens or carcinogens. Ames concluded, "Nature is not benign; no human diet can be entirely free of mutagens and carcinogens."[8] In fact, the very low concentrations at which most carcinogenic substances occur and the large number of anticarcinogens found in the diet minimize the overall hazard to humans.

TABLE 1.—*Dietary Recommendations of the American Cancer Society*

Avoid obesity
Cut down on total fat intake
Eat more high-fiber foods, such as whole grain cereals, fruits and vegetables
Include foods rich in vitamins A and C in the daily diet
Include cruciferous vegetables, such as cabbage, broccoli, brussels sprouts, kohlrabi and cauliflower in the diet
Be moderate in the consumption of alcoholic beverages
Be moderate in the consumption of salt-cured, smoked and nitrite-cured foods

Dietary Fats and Cancer

In the 1982 report of the National Research Council concerning diet, nutrition and cancer, fats were singled out as the factors for which the strongest association with cancer had been made.[9] Unsaturated fats contain one, two or more double bonds, and their usual source is vegetable oils such as safflower oil. Saturated fats, with no double bonds, are largely animal products (with notable exceptions such as coconut oil); examples include beef, butter, cheese and chocolate. It is of note that in the period 1963 to 1977, Americans decreased their intake of animal fats and oils by 47%, but increased their intake of vegetable fats and oils by 58%.

A large amount of experimental evidence has accumulated regarding dietary fats and cancer. The mouse mammary tumor system has been studied most extensively.[10] The incidence of tumors induced by chemicals or arising spontaneously in this system is increased by a high-fat diet, even with careful control of caloric intake by using isocaloric diets.

This experimental finding has been confirmed in numerous subsequent studies. In both rats and mice and with both spontaneous and induced mammary tumors, the animals fed a high-fat diet have more tumors, with earlier appearance of the tumors and more tumors per animal.[11] Given at high levels, polyunsaturated fats result in more tumor formation than do saturated fats.[12] The total amount of fat appears to be more important than the type of fat, as long as the animals are given a small supply of dietary essential fatty acids along with high amounts of dietary fat.[13,14]

The experimental data concerning fat and cancer are of greater interest because of epidemiologic evidence showing a strong positive correlation between the total amount of dietary fat available for consumption and the age-adjusted death rate from breast cancer.[15] A major problem with information of this type is that countries with a low incidence of breast cancer tend to be relatively underdeveloped, such that any variable related to economic development is likely also to be related to breast cancer incidence—indeed, there is also a linear correlation between the gross national product and the incidence of breast cancer.

For the period 1968 to 1972, the annual age-adjusted incidence of breast cancer in Miyagi, Japan, was 13 per 100,000, while the corresponding figure for Connecticut was 71.4 per 100,000. The risk in the US city was 5.5 times higher than that in Japan and increased to 8 times higher if

only postmenopausal women were studied. In two different surveys carried out in 1968 and 1969, Americans were found to consume three times the amount of fat as did the Japanese.[16]

The incidence of breast cancer has recently been increasing in Japan, with a doubling of mortality rates from this disease from 1955 to 1975. Surveys of various districts in Japan showed that the incidence in breast cancer rates correlated with those districts where fat intake had increased. In the 1950s to the 1970s there was an increasing westernization of the Japanese diet, with increased fat intake, increasing weight and an earlier onset of menarche.[17,18]

Several different mechanisms have been proposed for the relationship between dietary fat and breast cancer. These include hormonally mediated changes, fat-induced obesity itself, changes in immune response and changes in membrane properties. Hormonal changes have been studied in this regard.[19] In rats the enhancing effect of dietary fat appears to be mediated via prolactin,[20] but there has been no convincing evidence for a role of prolactin in humans. Estrogens assume particular importance in the current concepts of the possible role of obesity in postmenopausal breast cancer. Postmenopausal circulating estrogens are largely derived from the aromatization of androstenedione, resulting in the formation of the estrogen estrone. The principal site for this conversion is adipose tissue, and the composition of adipose tissue depends in part on the diet. The older and more obese a woman is, the greater her peripheral estrogen formation.[21] Studies looking at hormone levels in patients with breast cancer have had mixed results. Recently investigators have begun to measure hormone levels in breast secretions.

Dietary Fiber and Cancer

Of all areas of interest in this field, the one receiving the most media attention is the fiber hypothesis. One needs only to read the back of the morning cereal box to get the latest information from the National Cancer Institute on diet and cancer. Interest in the relationship between dietary fiber and large bowel cancer is largely the result of Dennis Burkitt's observation of low colon cancer rates in areas of Africa where fiber consumption and stool bulk are high.[22] Burkitt proposed that a high-fiber diet would effectively dilute out carcinogens. He found that African villagers had a stool bulk about four times that of English boarding-school pupils. The finding of increased stool bulk with high-fiber diets has since been confirmed by other authors and is thought to be due to indigestible fibers contributing directly to stool bulk as well as water adsorbed onto the fiber.

Burkitt and co-workers also proposed that diets low in fiber lead to a slow transmission of dietary components through the gut. The slow transit time may allow a longer time during which carcinogens present in the gut may be in contact with the gut wall.[23] The concept of a decreased transit time due to fiber intake has been questioned. Studies have shown that patients with a stool transit time of a day or less (comparable to the irritable bowel syndrome) actually have a longer transit time when fiber is added to their diet. Other aspects of Burkitt's fiber hypothesis have also been questioned, especially his emphasis on cereal fiber. African diets are actually low in cereal fiber, with most of their intake consisting of fruits and vegetables.[24] Also, despite the emphasis on the fiber they contain, fruits and vegetables are high in vitamins A and C, as well as other substances that may exert a protective effect.

One problem with interpreting the dietary fiber data is the wide variety of fiber types termed "dietary fiber," some more digestible than others. There are two major classes of fiber: polysaccharides and lignins. The most digestible fiber types are those found in fruits and vegetables; the least digestible are lignins, which are mainly found in cereal brans.

Results of experimental studies of the effect of fiber on colon carcinogenesis have been mixed, largely because of major differences in the fiber used in different animal species.[25] Epidemiologic studies have also been inconclusive. Fiber intake is generally higher in countries with a low incidence of colon cancer, but studies done in Canada, Puerto Rico and Hong Kong showed no protective effect of fiber. The protective effect is more readily seen in populations with a high fat intake, as in studies comparing the diet of rural Scandinavians (high fat, high fiber) with that of New Yorkers (high fat, low fiber) in which the latter had a higher colon cancer rate.[26] In one study done of American blacks in the San Francisco Bay Area, the relative risk of colon cancer among blacks with a low-fiber, high-fat diet was 2.68 times greater than in blacks with a high-fiber, low-fat diet.[27] Overall, epidemiologic evidence to date suggests that dietary fiber plays a role in protecting the colon against carcinogens, but that other factors may be equally or more important.

Dietary fats are thought to play an important role in colon cancer etiology. Epidemiologic correlations can be made between the amount of dietary fat available for consumption and colon cancer rates. Countries with a high rate of breast cancer commonly have higher rates of colon cancer as well. Experimental evidence suggests that rodents fed a high-fat diet have increases in colon cancers induced by various carcinogens. Unfortunately, many of these studies did not control for caloric intake.[28]

How do changes in diet affect colon cancer incidence? Primary and secondary bile acids are thought to play a role in colon carcinogenesis, not as inducers, but as promoters. The theoretic basis for the carcinogenic activity of the bile acids is their structural similarity to such hydrocarbons as methylcholanthrene, a known potent carcinogen, and the possibility of bacterial conversion of bile acids to carcinogenic compounds. The yield of chemically induced colon cancers in rats is significantly increased when bile acids are given intrarectally.[29] Bile acids alone produce no tumors, suggesting that the bile acids produce their effects as promoters. In the animal model, the carcinogenic effects of azoxymethane are increased by surgically diverting bile to the middle of the intestine, a procedure that increases fecal bile acids. An increase in fat in the duodenum is known to stimulate bile acid release, and a western diet has been linked to an increase in the fecal content of bile acids. A diet high in fat and low in fiber may also change gut flora towards more anaerobic bacteria that are better able to convert primary to secondary bile acids and are postulated to change bile acids to carcinogenic compounds.

Dietary Cholesterol and Cancer

Cholesterol is the obligate precursor of bile acids, a fact that is of greater significance in light of recent studies on cholesterol and cancer. Population studies have shown a strong positive correlation between the per capita consump-

tion of cholesterol and regional differences in colon cancer rates. Also, international rates of coronary artery disease mortality (linked to a high-cholesterol diet) are seen to be high in areas with high rates of colon cancer. Animal studies have shown cholesterol to be a potent dietary cocarcinogen.[30] Despite these facts, at least eight studies have shown a statistically significant inverse association between blood cholesterol levels and total cancer mortality, especially at cholesterol levels of less than 190 mg per dl.[31] Virtually all of the evidence relating blood cholesterol to the subsequent development of cancer is drawn from long-term prospective cohort studies in which cardiovascular disease was the end point of principal interest. One of the key questions is whether the inverse relationship reported in some of these studies could be due to the fact that these cohorts had persons with cancer at the time of entry, with already depressed cholesterol levels due to their cancer. If one eliminates persons who died within the first two years of their base-line studies, the inverse relationship persists in three studies—that is, a low serum cholesterol level associated with a subsequent higher cancer death rate. Not all published studies have shown such a relationship; in eight studies there was no relationship between a low serum cholesterol level and increased cancer mortality, and, in fact, two showed a trend toward a positive relationship.

An apparent paradox is raised by these data: the evidence from some prospective studies points to a possibly harmful effect of a low serum cholesterol level, yet the studies of diet point to a relationship between an increased intake of cholesterol and an increased cancer risk. It has been hypothesized that the relationship of cholesterol intake to cancer is found in a subgroup of the population with a high intake but low blood levels due to increased excretion of cholesterol.[32] An effort to reduce serum cholesterol levels by the use of clofibrate led to the unexpected result of a 25% higher mortality in the clofibrate group than in controls. A small part of this increase was due to more cancer deaths in the clofibrate group. Although not statistically significant, the 11 colon cancer deaths in the clofibrate group versus 6 in the controls raises a concern about a potentially harmful effect of exposing the colon to higher amounts of cholesterol.[33] Supplementing the diet with large amounts of polyunsaturated fats in rats caused a shift of cholesterol from the systemic circulation to the gut lumen and an increase in large bowel tumors.[34] It is clear that the cholesterol-cancer relationship is a complex one. Future studies should be done with a look not only at serum cholesterol levels, but at cholesterol excretion as well.

Cruciferous Vegetables and Cancer

In an attempt to better understand the relationship between diet and colon cancer, a large number of dietary surveys have been done. In spite of the many differences in design and method of selecting controls, several studies of diet reported by patients with colon cancer suggest a protective effect of vegetables. In addition to containing fiber and vitamins A and C, vegetables are also known to contain materials that are capable of inhibiting experimentally induced tumor formation. Human cells, especially hepatocytes, are well adapted to detoxify foreign compounds and to produce excretable metabolites. One prominent example is the mixed-function oxidase system, which has the ability to detoxify many of the known carcinogens. In nature there are numerous compounds with the capacity to induce the activity of these detoxifying systems and to inhibit experimental carcinogenesis.[35]

One of the best studied examples of this inducer phenomenon is seen in the vegetables of the Brassicaceae family, such as brussels sprouts, cabbage, cauliflower and broccoli. These vegetables contain large amounts of indoles, which are known to induce increased activity of the mixed-function oxidase system that breaks down polycyclic aromatic hydrocarbons. Studies of animals have shown that increases in this activity can protect against neoplasia induced by hydrocarbons.[36]

Vitamins, Minerals and Cancer

The American Cancer Society recommends including foods rich in vitamins A and C in the diet, a recommendation that is derived from recent work done in the area of "chemoprevention." Chemoprevention is a rapidly growing area of research based on the concept that the public is more likely to accept prescription than proscription—that is, would rather add to the diet than to take away. In addition to vitamins A and C, vitamin E and the trace mineral selenium are thought to have potential roles in preventing cancer.

As seen in Table 2, the "conservative" recommendations for cancer prevention involve ingesting doses higher than the recommended daily allowance of these substances, an important fact, as each is potentially harmful at very high doses.[37] Preformed vitamin A is found in liver, butter, whole milk, cheese and egg yolk, and vitamin A's precursor β-carotene is found in green and yellow vegetables. Although a sustained high intake of β-carotene leads only to reversible skin discoloration, long-term doses of vitamin A of more than 25,000 IU per day result in significant toxicity, which may include exfoliative dermatitis, dry mucous membranes, headaches, emotional lability, fatigue, epistaxis, edema and liver function abnormalities with hepatomegaly. Vitamin E is the least toxic of the fat-soluble vitamins, but doses of higher than 1,200 IU per day are reported to cause nausea, diarrhea, intestinal cramps, skin reactions, myopathy and gonadal dysfunction. Although most patients taking high doses of vitamin C have no side effects, doses of 2 to 10 grams or more daily may result in acidosis, oxaluria, diarrhea and nephrolithiasis. Like vitamin A, selenium at high doses can lead to serious and irreversible side effects, including multiple dermatologic abnormalities and peripheral nervous system dysfunction.

Oxygen-free radicals are thought to be a common mechanism through which many carcinogens act. Vitamins C and E, β-carotene and selenium are all known to protect against free radical damage.[38] In addition, vitamins C and E inhibit nitrosamine formation. The role of vitamin E in preventing human cancers is largely unexplored, and the modifying effects of vitamin E in animals treated experimentally with carcinogens have been variable. Much more work has been done with vitamin C, with protective effects seen in human stomach, esophageal and laryngeal cancers, as well as cervical dysplasia. Linus Pauling and others have examined the possible role of vitamin C in extending survival in advanced cancer. In a series of 100 cases compared with 1,000 historical controls drawn from a review of records, they claimed a striking survival advantage in their patients given 10 grams of vitamin C daily.[39] This work has been questioned, and recent double-blind, randomized studies done at the Mayo Clinic

TABLE 2.—*Dietary Intake of Vitamins A, E and C and Selenium in Preventing Cancer**

Nutrient	*RDA*	*Conservative Recommendation for Cancer Prevention*	*Serum Levels of Possible Toxicity*
Vitamin A, IU	5,000	12,500	Limited: long-term intake 25,000/d; short-term intake 300,000-1,000,000
Vitamin E, IU	10-20	200-800	Negligible: 1,200
Vitamin C, mg	60	1,000	Negligible: 1,000-2,000
Selenium, μg	None	50-200	Significant: 200

RDA = recommended daily allowance

*Adapted from Watson and Leonard.[37]

have shown no prolongation of survival in patients with advanced cancer given the same dosages of vitamin C.[40]

Selenium, an essential trace element, has a key role in the activity of the enzyme glutathione peroxidase, which protects against oxidative damage to cells. Both internationally and in the United States, geographic areas with low selenium levels in the soil or in blood specimens have higher cancer rates than in high-selenium areas; the strongest inverse relationships are seen with breast and colon cancer. These data should be interpreted cautiously, however, as high selenium levels in soil tend to occur in more rural areas, and variables other than selenium may be more important. Experimental evidence, however, points to a possible anticarcinogen role for selenium. In tissue cultures, selenium reduces the metabolic activation of certain carcinogens, altering the pattern of degradation to less toxic metabolites. In a large number of animal experiments, using a wide variety of inducing agents, selenium-supplemented animals have had tumor incidences approximately half those of control animals.[41] Overall, selenium remains an intriguing possible chemopreventive agent, but toxicity currently limits its use to the experimental setting.

Some of the most exciting research in the area of chemoprevention has been done with the retinoids. The precursor of vitamin A is β-carotene, the major carotene in the diet. β-Carotene can be oxidized to the aldehyde retinal, then to the alcohol retinol. Naturally occurring retinols are toxic in humans if ingested in high doses, so that a number of retinol analogues have been studied, especially all-*trans*-retinoic acid, 13-*cis*-retinoic acid and etritinate.

The results of many epidemiologic surveys imply that there is an inverse relationship between some forms of cancer and the intake of β-carotene as well as of retinol. Possibly β-carotene itself exerts a protective effect, as it is known to be a potent free radical scavenger.[42] Studies have shown that a matched population with a lower consumption of vitamin A had an increased incidence of lung cancer. This type of study has also shown positive results in patients with esophageal, laryngeal and bladder carcinoma. Other data, such as those from the Hypertension Detection and Follow-up Program, have failed to show a relationship between retinol and retinol-binding protein and the subsequent development of malignancy over the next five years.[43] Possibly the most important question of all concerns the issue of cancer prophylaxis with vitamin A analogues in the general population. The National Cancer Institute is currently funding about 16 studies of the use of vitamin A analogues or β-carotene in either the general population or in high-risk groups to test a possible lowering of cancer mortality.

TABLE 3.—*Overview of Diet's Role in Cancer*

- Diet may be a factor in as many as 35% of all cancers
- No diet is free of all known mutagens and carcinogens
- Intake of dietary fats, both saturated and unsaturated, should be decreased from America's current level of 40% of caloric intake
- Dietary fiber probably plays a role in protecting the colon against carcinogenic challenges, but other factors may be equally or more important
- Diets should contain foods high in vitamins A and C and in cruciferous vegetables, but vitamin supplements should be used with caution

Regardless of the outcomes of these studies, it is clear that study of the relationship of vitamin A and cancer on an experimental level can teach us something about the basic processes of carcinogenesis.[44]

Retinoids are potent agents for controlling cellular differentiation and proliferation. Data gathered from animals exposed to carcinogens or from carcinogens added in tissue culture systems almost universally support a preventive role for vitamin A and other retinoids in cancer development. Vitamin A deficiency produces squamous metaplasia; excess vitamin A leads to mucous metaplasia in previously normal keratinized squamous epithelium. The premalignant phenotype of mouse prostate glands that have been treated with the carcinogen 3-methylcholanthrene can be altered by retinoids. The atypical epithelial cells that are induced by the carcinogen disappear on retinoid treatment of the organ cultures and are replaced by cells with more normal morphology.[45]

In cell culture studies, retinoids can be clearly shown to be suppressors of the malignant phenotype in cells previously treated with carcinogens. Removing the retinoids allows expression of the transformed state. Even more promising, retinoids can change the differentiation of invasive neoplastic cells growing in culture. For example, in the human promyelocytic leukemia system, retinoids can induce terminal differentiation of malignant leukemia cells, leading to formation of morphologically mature granulocytes, which have functional markers of mature neutrophils.[46] In summary, retinoids can suppress experimental carcinogenesis in vivo, can suppress development of the malignant phenotype in vitro and can even exert effects on some fully transformed and invasive neoplastic cells.

Conclusions

A cautious observer would conclude that more research in the area of diet and cancer is needed. If one looks at smoking and lung cancer as a model, however, it is reasonable to

change behaviors before all of the data are available, potentially changing the cancer risks for millions of people. Table 3 outlines several recommendations based on currently available data.

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Epitomes

Important Advances in Clinical Medicine

Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in allergy that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Mental Effects of Long-term Theophylline Therapy in Children

THEOPHYLLINE is the most widely used drug in the United States for the control of chronic asthma. Its use has benefited most persons with this condition. It has an unusually narrow therapeutic index, however, and its use is associated with an increasing number of reports of acute toxic reactions. Central nervous system toxicity occurs with overdosage or by extraneous or intrinsic factors that retard theophylline clearance in patients receiving adequate and proper dosages. Nervousness, restlessness, insomnia, tremors, headaches and convulsions are often noted with high theophylline serum levels.

There have been few reports published of more subtle mental effects, even though many clinicians report cases of such effects anecdotally. Published reports include speech defects; episodic bizarre behavior described as "theophylline madness"; exacerbation of spasticity, depression, behavior or learning problems (or both), and sleep disruption. Considering the widespread use of theophylline, it is surprising that controlled studies have not long since been done of the effects of this drug on brain function.

A retrospective survey has been done of possible adverse behavioral effects of theophylline use in a large group of children with asthma. This showed a significant correlation between theophylline use and inattentiveness, hyperreactivity, irritability and difficult and "withdrawn" behavior.

More recently, in fully controlled trials, theophylline has been shown to adversely affect brain function as measured by a number of sensitive psychological tests such as the Selective Reminding test, the Benton Visual Retention test, the Stroop test and parents' and teachers' child behavior checklists.

In one study a significant improvement in psychological test results occurred when children with asthma were switched from theophylline to cromolyn sodium therapy. These tests reflected visual-spatial planning but were only seen in patients with lower IQ scores (87 to 105) and not in those with IQs in the 111 to 134 range.

Another study showed a correlation between depression and the length of time children had been taking theophylline. The study design, however, did not permit discrimination between an asthma effect or a drug effect as the more likely precipitant.

These and other evaluations have provided evidence that the use of theophylline adversely and significantly affects cognitive ability, especially in terms of short-term memory and concentration, school performance and behavior of some children.

Studies of caffeine intake, which is closely related, have shown that tolerable doses of caffeine in the short term increase the capacity for sustained intellectual effort and decrease reaction time. Higher doses and long-term consumption of caffeine, however, cause a worsening of delicate muscular coordination and accurate timing, restlessness, disturbed sleep and irritability.

The controlled studies of the use of theophylline and the similar well-studied effects of caffeine ingestion question the wisdom of prescribing ongoing theophylline therapy for certain children. It is now clear that physicians need to ask specifically about behavior, school performance and sleeping patterns to assure safety with theophylline and that parents should be advised of possible side effects with its use. A switch to an alternate therapy on a trial basis should be considered in any questionable instance.

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The Management of Asthma During Pregnancy

ASTHMA is probably the most common potentially serious medical condition to complicate pregnancy. Retrospective studies suggest that maternal asthma increases the incidence of preterm births, infants with low birth weights and perinatal deaths. Although confirmatory data are lacking, the accepted working hypothesis is that adequate control of asthma during pregnancy is the most important factor in reducing this excess risk.

Optimal management of asthma during pregnancy may involve environmental control measures, immunotherapy, medication or a combination of these approaches. Decreased exposure to avoidable triggering factors (household pets, other allergens, smoking) is an obvious, but sometimes underused, therapeutic modality. Immunotherapy is considered safe during pregnancy in women who are already deriving benefit from it; conservative dosing is recommended to minimize the chance of an anaphylactic reaction. The benefit-risk ratio does not usually favor beginning immunotherapy during pregnancy.

Pharmacologic management of asthma during pregnancy is more problematic because no asthma medication can be considered proved safe during pregnancy according to the recent Food and Drug Administration (FDA) pregnancy classification. There are a number of asthma medications, however, that appear to involve less risk during pregnancy than the risk of the uncontrolled asthma that could result if they were not used. Reassuring data in humans are available for ephedrine, theophylline, cromolyn sodium, beclomethasone dipropionate and prednisone/prednisolone. In addition, terbutaline sulfate has been used extensively in the management of premature labor, although there are no reported data in humans during early pregnancy. Inhaled bronchodilators are recommended by some authors because of their topical route and, in the case of terbutaline, the favorable FDA pregnancy classification based on reassuring animal data. The optimal sympathomimetic drug of choice for the treatment of acute asthma during pregnancy (parenterally given epinephrine or terbutaline, or mechanically nebulized bronchodilators) is not uniformly agreed upon, but, as noted above, adequate control of the asthma is the most important challenge in that situation.

Although pharmacokinetic changes have been reported to occur during pregnancy, theophylline is the only asthma medication for which gestational pharmacokinetic data are available. One study of ten pregnant women with asthma suggests that the clearance of theophylline may be prolonged during later pregnancy but that the weight-corrected volume of distribution does not change during pregnancy. Thus, the recommendations for milligram-per-kilogram loading doses of theophylline do not need to be altered during pregnancy, but maintenance doses may need to be reduced. Because the data reveal significant interpatient variation in gestational theophylline pharmacokinetics, determining theophylline concentrations at least once each trimester is recommended in pregnant patients receiving theophylline regularly.

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Nonsedating Antihistamines in the Treatment of Allergic Disease

ALTHOUGH THE EFFECTS OF HISTAMINE have been known for 75 years, it was not until 1937 that Daniel Bovet was able to antagonize this mediator with the first antihistamine, compound 929F. Although he received a Nobel prize for his work, this compound was too toxic for human use. Now, more than 50 different antihistamines in six different classes are available by prescription or over the counter in the United States.

We now know that there are H_1 and H_2 histamine receptors, but we are most concerned with H_1 receptor activity in cases of allergy, whereas H_2 receptors primarily regulate gastric secretion of hydrochloric acid. The effects of classic antihistamines on H_1 receptors in the central nervous system, with resulting sedation and their anticholinergic effect on mouth dryness, limit their usefulness in many patients. The unwanted effects of sedation are due primarily to the lipid solubility of these older compounds, which allows them to cross the blood-brain barrier into the central nervous system and affect the H_1 receptors in the brain. The newer nonsedating antihistamines are often analogues or even active metabolites of classic antihistamines. Their molecular structure, however, interferes with passage into the brain. Many of the new nonsedating antihistamines are currently under clinical development, but three drugs—astemizole, mequitazine and terfenadine—are available for use in many countries.

In May 1985, terfenadine (Seldane) was approved for use in the United States as a 60-mg tablet to be administered twice a day for the treatment of seasonal allergic rhinitis. This compound has been shown to be an effective H_1 receptor antagonist for most patients with allergic rhinitis. In clinical trials, the incidence of sedation has been no greater than that reported by patients taking a placebo. Twice-a-day dosing increases patients' compliance, and the lack of central nervous system and anticholinergic side effects encourages continued use. Activity is seen in most patients after a single dose, but maximum response may not occur for three days.

Astemizole is currently available in many countries as a 10-mg tablet and should be given approval by the Food and Drug Administration for use in the United States by spring

1987. This compound has a very strong affinity for H_1 receptors and a half-life of several days, which accounts for its long duration of activity. This effect permits once-a-day dosing, but it may result in the prolonged inhibition of immediate hypersensitivity skin test reactions. The drug has been effective in treating chronic urticaria and allergic rhinitis. A somewhat slow onset of activity in some patients may be overcome by giving a loading dose of 20 to 30 mg a day for the initial one to three days of therapy.

Mequitazine is a nonsedating antihistamine that has a somewhat narrow therapeutic-to-sedation range. It, too, has a slower onset of activity than terfenadine, but it has been used successfully in Europe for controlling allergic symptoms. Recent studies indicate not only that it is an antagonist of histamine but that it also has the capacity to inhibit mediator release. There are currently no ongoing clinical trials in the United States, so its availability in this country is uncertain.

Most clinical studies with the new nonsedating antihistamines have shown them to be as effective as classic antihistamines in controlling the symptoms of allergic rhinitis. Not all patients respond, however, or respond equally. Furthermore, it appears that some patients whose symptoms are adequately controlled during periods of moderate antigen exposure derive less benefit during peak periods of antigen concentration. Some of these compounds have a longer duration of action, which has raised the question of cumulative effects with prolonged use. There is currently no evidence of this in standard patient care, but the possibility may exist in cases of drug overdose.

At least five other nonsedating antihistamines are under development in the United States. Some of these can be administered once a day, others will be available in a liquid formulation for children and some will be combined with a systemic decongestant such as pseudoephedrine.

The advent of these newer nonsedating antihistamines will offer physicians a wider choice of medication to inhibit the adverse effects of histamine in their allergic patients. Because antihistamines only block the effect of histamine, however, for some patients greater relief of symptoms awaits the development of medications that can prevent or modify the release of, or the effects of, the other mediators of the allergic response. Nevertheless, this new class of nonsedating antihistamines allows the almost 50% of all allergy patients who report sedation from classical antihistamines the opportunity to obtain relief without significant side effects.

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Neuropeptides

THE MECHANISMS by which functionally distinct cells communicate and in the process regulate their physiologic capacities is one of the most active areas of experimentation in modern biology. Early investigations showed that neuropeptides, hormones and lymphokines mediated diverse intercellular modulatory functions in separate systems such as the central nervous, endocrine and immune systems, respectively. It is now clear, however, that bidirectional communication between each of these three systems occurs, and, in the case of neuroimmune interactions, lymphokines such as interleukin 1 and 2 may activate glial cells and astrocytes, whereas neuropeptides have now been shown to modulate immediate hypersensitivity and cell-mediated immune responses.

Neuropeptides released from peripheral sensory nerves including substance P, vasoactive intestinal peptide and somatostatin are potent mediators of smooth muscle and vascular functions. Substance P has been observed to contract intestinal smooth muscle, produce the vasodilation of systemic arterioles and increase the secretion of glycoprotein-rich fluid from human tracheal epithelium, whereas the vasoactive intestinal peptide causes intestinal smooth muscle relaxation and increased vasodilation of cutaneous microvessels. These effects may contribute to the plasma extravasation and alterations in blood flow that accompany inflammatory responses.

The modulation of immediate hypersensitivity reactions by neuropeptides is suggested by the elevated local tissue concentrations of peptides such as substance P and somatostatin detected during acute responses. In vitro studies have shown that substance P acts selectively on mast cells, but not basophils, by an IgE-independent mechanism to cause the release of histamine, leukotrienes and other mediators. In contrast, somatostatin expresses only minimal mast cell-activating activity and may modulate hypersensitivity reactions by indirect mechanisms by inhibiting the release of mediators from immunologically activated basophils.

An understanding of the mechanisms by which neuropeptides alter cell-mediated immune responses has been derived principally from in vitro experimentation. Peptides such as somatostatin and vasoactive intestinal peptide show mainly inhibitory effects on T- and B-lymphocyte activities such as proliferation and immunoglobulin synthesis, respectively. These responses are thought to be mediated by the elevation of intracellular 3′:5′-cyclic adenosine monophosphate levels in response to the neuropeptides binding to specific cell-surface receptors. In contrast, substance P has been shown to exert a stimulatory influence on T-lymphocyte proliferation and to increase the production of IgA from gut-derived lymphocytes. Experiments suggest that these substance P effects are also receptor mediated and are a result of substance P-induced activation of the phosphatidylinositol pathway in a distinct subset of lymphocytes.

The concept of the possible participation of neuropeptides in the pathogenesis of certain disease states has come largely from their chemical or immunochemical detection in tissue extracts or fluids, or by showing that locally administered neuropeptides mimic the features of hypersensitivity. Substance P has been detected in the nasal secretions of humans with allergic rhinitis and in the tissues of patients with urticaria. Its role in these conditions, however, and in other disease states where its immunopathologic role has been suggested, such as in arthritis and asthma, has yet to be conclusively determined. Progress in our understanding of how neuropeptides modulate neuronal and nonneuronal homeo-

static responses will be largely determined by the identification and purification of specific neuropeptide receptors, the in situ analysis of receptor and receptor-gene regulation and the design of novel pharmacologic agonists and antagonists based on our understanding of receptor stereospecificity.

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Compliance in Taking Medications

MEDICAL COMPLIANCE has become a major factor in treating chronic disease. It is estimated that 50% of patients do not comply with their medical regimens. Noncompliance is especially a problem in treating patients with allergic disorders, as they frequently must take medication even when they are feeling well.

Compliance will vary in direct proportion to patients' understanding of a medical problem, their perceived benefit of a therapeutic plan, the possibility of medication side effects, the inconvenience of a therapeutic regimen and its cost.

To decrease the incidence of side effects, a new medication regimen should be initiated with the lowest dose possible, then the dosage titrated slowly up to the optimal therapeutic range (unless side effects occur). Potential side effects should be explained to patients. A written sheet, such as the American Medical Association's patient medication instructions or one designed by the physician, should be given to the patient.

It is important for physicians to explain simply why patients must take their medication in a specific manner. This explanation should be given in lay terms, and patients should be provided with clearly written instructions, including the name of the medication, its dosage and schedule.

A practical way to provide these written instructions is through the use of an inexpensive wallet-sized card called the Medical Management Card. This card has been used with success for years at the allergy clinic of the University of California, Irvine. Complimentary copies of the Medical Management Card can be obtained from Mark Havel, Tri-City Medical Center, 4002 Vista Way, Oceanside, CA 92056 or local Key Pharmaceutical representatives.

In addition to the above, using a simplified drug regimen that, where possible, emphasizes the use of once-a-day or twice-a-day medication will greatly increase the probability that a patient will use the medication regularly. Prescribing Uniphyl, a once-a-day theophylline compound, can facilitate compliance and will still be as efficacious as the standard twice-a-day theophylline preparation, Theo-Dur. Theophylline compliance can be monitored by using Acculevel assay, which gives results in 30 minutes.

A simplified drug regimen is especially important in the school-aged population, where medication is frequently missed if a dose has to be taken at school. In younger children (who are often unable to swallow a tablet), it is frequently difficult to administer a liquid preparation because of taste, problems with spillage and problems with dosing. Therefore, the use of a beaded capsule sprinkled over applesauce or other foods is frequently more convenient.

Physicians should be aware of the economics of a therapeutic plan, but not use generic substitutes to save costs if those products will not have the same therapeutic efficacy as the brand-name medication. This may be especially the case for certain long-acting, sustained-release theophylline preparations.

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Indications for Giving Immune Globulin Intravenously

THE CURRENT AVAILABILITY of safe intravenous immune globulin preparations has led to applications in various clinical situations. Intramuscular preparations have been used for decades for replacement therapy in antibody deficiency states, but only relatively small doses are tolerated. There is a delay in absorption from the injection site, and some proteolytic degradation may occur before the immunoglobulin is absorbed into the bloodstream. These problems do not exist with intravenously administered immune globulin.

Immune globulin therapy is indicated in patients with humoral immune defects who are unable to produce adequate amounts of IgG (serum IgG levels less than 400 mg per dl in older children and adults or a proved subclass deficiency). Immune globulin given intravenously is preferable to intramuscular preparations in patients with limited muscle mass or bleeding tendencies, those needing large, rapid increases in their serum IgG level or those in whom intramuscular therapy is poorly tolerated. Doses should be individually tailored to a patient's clinical response because susceptibility to infection does not always correlate with IgG serum levels. Generally, levels within one standard deviation of normal for a patient's age can be attained with 150 to 300 mg per kg body weight of immune globulin given intravenously every three weeks, depending on a patient's rate of catabolizing the immune globulin. Deficiency of one or more IgG subclasses in a patient with severe or recurrent infections can be successfully treated with intravenous administration of immune globulin provided the preparation contains adequate concentrations of the deficient subclass(es). Preparations with an IgG subclass distribution similar to that in normal human serum are preferable and are currently available in the United States from Cutter, Hyland and Sandoz laboratories. Prophylaxis or therapy with intravenous immune globulin may also be indicated when

there is a defect in a specific antibody formation to a particular infectious agent.

Immune globulin given intravenously in high doses has been found to promote a rapid rise in the platelet count in as many as 75% of patients with idiopathic thrombocytopenic purpura (ITP). Splenectomy can often be avoided or postponed in patients unresponsive to steroid therapy who would otherwide need an operation. Response rates and length of remission are more favorable in acute childhood forms of ITP. It is difficult to maintain remission in some cases of chronic ITP unless repeated doses of intravenous immune globulin are given, and this can become expensive and time consuming. Because it is not possible at this time to predict which patients with ITP will respond to immune globulin given intravenously, it may be administered when there is risk of life-threatening hemorrhage (platelet count $< 20,000$ per μl), during preparation for an operation, to control platelet deficiency hemorrhage or to avoid a splenectomy. Some patients who fail to respond to splenectomy benefit from intravenous immune globulin therapy. Immune globulin has been used in treating ITP during pregnancy, being administered to a mother before delivery and to a thrombocytopenic infant during the first several weeks of life until the platelet count has become stable.

Anaphylactic reactions have been associated with the intravenous administration of immune globulin in some patients with total IgA deficiency. These patients often form IgG, IgM or IgE (or all three) antibodies against the IgA present in many intravenous preparations of immune globulin. IgE antibodies appear to correlate best with the occurrence of anaphylaxis. If such therapy is indicated in such a patient, an intravenous preparation of immune globulin with a very low content of IgA should be used, preferably less than 5 μg per ml. At present, one preparation meeting this criterion is commercially available (Gammagard, Hyland).

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Leukotrienes

THE LEUKOTRIENES are a family of potent mediators of hypersensitivity and inflammation that are derived from the 5-lipoxygenation of arachidonic acid in mast cells, mononuclear phagocytes and polymorphonuclear leukocytes. Beyond a source in leukocytes and other inflammatory cells and the presence of three conjugated double bonds, for which the family name was selected, the leukotrienes share the same biosynthetic precursor, a requirement for additional polar substituents for expression of activity and oxidative mechanisms of inactivation. The parent 5,6-epoxyeicosatetraenoic acid, termed leukotriene (LT) A_4, is converted enzymatically either to a 5-hydroxy-6-*S*-glutathionyleicosatetraenoic acid designated leukotriene C_4 (LTC_4) and then by peptidolysis to the other sulfidopeptide leukotrienes LTD_4 and LTE_4 or to a 5,12-dihydroxyeicosatetraenoic acid called LTB_4. The principal pathway of inactivation of LTC_4, LTD_4 and LTE_4 is by peroxidation to the respective sulfones and of LTB_4 by ω-oxidation to 20-hydroxy-LTB_4 and 20-carboxy-LTB_4. Each of the leukotrienes now can be extracted and isolated in high yield by liquid chromatography and quantified by specific and sensitive radioimmunoassays.

LTC_4, LTD_4 and LTE_4 are potent vasoactive and smooth muscle contractile factors that together constitute the slow-reacting substance of anaphylaxis. Maximal constriction of human bronchi is evoked by concentrations of the sulfidopeptide leukotrienes 1/10,000 to 1/100 that of histamine. In addition, the pulmonary airway constriction is maintained for a longer time when the stimulus is leukotrienes than if it is histamine. Concentrations of sulfidopeptide leukotrienes too low to elicit bronchial constriction may decrease the threshold for responses to subsequent stimuli and thus create a hyperirritable state, as in asthma. LTB_4 is the most potent stimulus of polymorphonuclear leukocyte chemotaxis and other functions to be generated from arachidonic acid. LTB_4, like prostaglandin E_2, is immunosuppressive by way of specific actions on regulatory T lymphocytes. The effects of leukotrienes on leukocytes, blood vessels, smooth muscles and other tissues is mediated by distinct subsets of cellular receptors.

Leukotrienes are detected in tissues and fluids in relation to the expression of several types of hypersensitivity and inflammatory reactions. In the skin, LTB_4 predominates in patients with psoriasis and LTC_4 in cases of allergic reaction elicited by pollen proteins. LTC_4 and LTB_4 are found in the fluid of pulmonary airways of patients during attacks of asthma, whereas LTD_4 and LTE_4 attain high concentrations in cases of adult respiratory distress syndrome. LTB_4 is the principal mediator of neutrophilic reactions, as are typical of gout and spondyloarthritis. Although the establishment of functionally relevant concentrations of leukotrienes in these diseases is temporally related to the tissue reactions, no inhibitors or antagonists of sufficient specificity to confirm the relationship have been applied systematically.

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Childhood Asthma and Sinus Disease

TRIGGERING FACTORS that aggravate bronchial reactivity in patients with asthma continue to be described. In young children, lower respiratory tract infections, especially those due to respiratory viruses, are the most common inciting events; in older children, environmental allergens take on greater

importance. The adverse effect of sinus disease on the stability of asthma has been described previously in adults, but only recently has this association been documented in children. In children with lower reactive airways disease, more than 50% have sinus radiographs that are abnormal, with a significant minority showing total opacification of one or more of their sinus cavities. The cases of 48 children (mean age 8.2 years) have been described with chronic (more than three months) reactive airways disease and evidence of chronic sinusitis on sinus radiograph; all had been receiving bronchodilators for at least three months with poor control of the asthma, and 18 had received corticosteroids; 14 were nonatopic. With appropriate antimicrobial management, 39 responded both clinically and radiologically. In some children previously requiring daily antiasthmatic medications, including corticosteroids, these medication regimens were able to be completely discontinued following the resolution of their sinus infections. Other investigators have found not only a reduced requirement for antiasthmatic medications, but also a substantially increased responsiveness to bronchodilator therapy.

Because the clinical signs and symptoms of sinusitis can be varied and at times quite subtle, physicians must rely on other diagnostic aids to establish a diagnosis and assess the adequacy of treatment. The sinus radiograph remains the gold standard for diagnosing sinusitis. There is no universal agreement as to how many radiographic views constitute an adequate examination. In children, however, a Waters view may be sufficient. This view clearly shows the maxillary sinuses are involved in about 90% of sinus infections, which may be due to the fact that their ostia are located high on the medial walls where gravitational forces oppose the upward movement of secretions. The Waters view also is useful for showing the frontal sinuses, and some assessment can be made of the ethmoid air cells. The radiographic signs that most closely correlate with positive bacterial aspirates are opacification, air-fluid levels and mucoperiosteal thickening of the mucosal lining. There is always some disagreement as to what degree of mucosal thickening is significant; we feel that at least 4 mm of thickening should be shown to be considered abnormal.

The bacterial characteristics of sinusitis are derived primarily from maxillary antral aspirates and from surgical mucosal specimens. The most common organisms in children with sinusitis are similar to those found in patients with acute otitis media: *Streptococcus pneumoniae, Hemophilus influenzae* and β-hemolytic streptococci; *Branhamella catarrhalis* has been increasingly found in young patients. Furthermore, anaerobic organisms are also commonly cultured when the appropriate media is used. Amoxicillin has proved to be an effective drug and has an 80% cure rate; similar results have been obtained with ampicillin, tetracycline, doxycycline and cefaclor, but penicillin and other cephalosporins are much less effective. Using a combination of erythromycin and sulfisoxazole may be appropriate when amoxicillin treatment fails and there is a suspicion of β-lactamase-producing *B catarrhalis* or *H influenzae*. Under these circumstances, other desirable agents include trimethoprim-sulfimethoxazole and a combination of amoxicillin and clavulanic acid. The appropriate duration of therapy has not been accurately determined, but recent studies indicate that at least three to four weeks are required to effect major radiologic and clinical improvement. If such improvement does not occur after three weeks, it is reasonable to change the antibiotic therapy. If evidence of bronchial hyperreactivity persists in the presence of an unaltered radiograph, antral lavage should be considered; more extensive surgical intervention, such as antral windows, would depend on many variables such as patient age, asthma stability and the location and extent of the disease process.

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Late-Phase Reactions and Chronic Asthma

CHRONIC ASTHMA is characterized by successive attacks of coughing or wheezing, often after respiratory infections. There is usually no obvious correlation to an immediately preceding allergen exposure. Usually minor respiratory irritants, however, such as passive smoking, strong perfume or cooking odors, may cause symptoms. Between attacks, the symptoms may not clear completely, and impaired pulmonary function for airway patency—as determined by the forced expiratory volume in one second (FEV_1), the peak expiratory flow and the maximum midexpiratory flow rate at between 25% and 75% of the values—may persist. Many patients have a few positive immediate skin tests, especially to house-dust mite, cat, pollens and molds, exposure to which does not necessarily correlate with attacks. On provocative inhalation challenge with such an antigen, however, many patients experience a moderate immediate bronchospasm (early phase) that subsides within 30 to 60 minutes, followed in 6 to 8 hours by a more severe bronchospasm, the late-phase asthmatic response (LAR), which is more persistent; these subjects have been called dual responders. Some patients with asthma, however, experience only the early response and others have minimal early but profound LAR. Pretreatment with classic bronchodilators (β-adrenergic agents and theophylline) before challenge can prevent the early response, but is less useful in LAR. Pretreatment with corticosteroids prevent or ameliorate only the LAR, while cromolyn sodium pretreatment blocks both early- and late-phase responses.

Studies in allergic humans and dogs suggest that in many, but not all, allergic persons, the combination of antigen and IgE antibodies on mast cells releases histamine, producing a transient reaction. Such activated mast cells, however, release chemotactic mediators, such as leukotriene B_4 and neutrophil and eosinophil chemotactic factors of anaphylaxis, which attract neutrophils and eosinophils into the inflammatory sites in bronchi and skin. These inflammatory cells release their granular contents, such as neutrophil oxidation products, eosinophil basic proteins that damage the tissues

locally. This tissue damage is responsible for the nonspecific hyperirritability of the airways causing chronic asthma. This has therapeutic implications, for these late-phase reactions respond to corticosteroid and cromolyn therapy, but less well to classic bronchodilators. Patients with asthma who have late-phase reactions may respond better to specific immunotherapy than do those who have only immediate early asthmatic responses. This supports the efficacy of immunotherapy in chronic asthma.

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Editorials

$250,000—Was It Worth It?

THE FINAL PARAGRAPH in a case report appearing elsewhere in this issue raises a troubling question. A 34-year-old man with a history of intravenous drug abuse was treated and cured of nine separate episodes of endocarditis between 1972 and 1984, when his cultures for pathogens remained sterile after he said he had discontinued intravenous drug use. He had been in hospital for more than a full year out of the past 12 and it was estimated that this patient received almost $250,000 worth of health care.

$250,000—Was it worth it? The final outcome is surely a major medical success story. Nine separate episodes of endocarditis caused by a variety of pathogenic organisms were each separately cured. After 12 years in and out of hospital this patient finally desisted from his intravenous drug abuse and has presumably been well since. The goals of health care for this patient were achieved in truly spectacular fashion.

But a nagging problem persists. Is this the best value that could be got for $250,000 in health care? No one would have said not to treat this patient, even so heroically. But was it worth it, or did others, who perhaps did not abuse themselves at public expense, not get health care they needed because public funds were not available? Questions such as these will not soon go away.

MSMW

Demographic Changes and Health Professions Education

CONVENTIONAL WISDOM hath it that there are now enough, and perhaps too many, physicians and other health professionals in practice, or there will soon be, and that it is time to cut back substantially on health professions education. This conventional wisdom assumes that the free market will supply the unmet health care needs for medically underserved "minority" ethnic groups and distribute health care providers more evenly to the medically underserved inner-city and remote rural areas. But if one delves a little deeper, one finds that many "majority" health professionals find themselves poorly trained to practice where the needs are greatest and that they tend to congregate in places and situations where they feel more comfortable with their "majority" background and training. In any case, improvement in the health status of the medically underserved has been disappointingly slow.

These problems are further exacerbated by a changing demography, particularly in the West. In California, at least, the ethnic minorities in the aggregate will become the numerical majority during the practice lifetime of many physicians and other health professionals who are in practice today. At the same time, another minority, the elderly in the population, is beginning to increase dramatically in both age and numbers. Many of these will also be medically underserved, unless something is done in the area of health professions education and training.

Elsewhere in this issue, Davidson and Montoya address one aspect of this problem. They have shown that the recruitment and training of minority health professionals can bring about a better distribution of health care to medically underserved populations. This is an important observation and one senses that when enough minority physicians and other health professionals are recruited and trained, so that the proportion of minority health professionals in a minority ethnic population more nearly matches the proportion of all health professionals to the general population, much of this problem will be solved. These recruitment and training efforts should and will continue, but it will be some time before any sort of numerical match occurs.

But what can be done more quickly to improve health care for medically underserved groups or populations? Can something be done through a cooperative effort? Who has a stake in this? Can health professions education help to address this problem? Clearly the communities with medically underserved populations have a stake. So do the health professions. So do the institutions that educate and train health professionals and prepare them for practice. And so does government. The evidence is accumulating that cooperative efforts among these parties at interest can occur, and when they do, they can make a difference in health professions education and in health care in medically underserved communities. In these areas of growing health care needs and in this era of growing technologic, social, economic and political interdependence, cooperative approaches among the interested parties may well be the way to go. The opportunities to improve the education and training of health professionals for practice in and with medically underserved communities are great. These efforts to improve health care for the medically underserved should be given the collaborative support that is needed. It can make a difference, and probably a great difference, if done with the full support of all concerned.

MSMW

Intestinal Manifestations of the Acquired Immunodeficiency Syndrome

DURING the past five years, the world has witnessed the emergence and spread of a new syndrome, AIDS. The causative agent, the human immunodeficiency virus (HIV), is a retrovirus that infects T-helper lymphocytes as well as other cells and produces a progressive deficiency of cellular immune function. While the precise pathogenetic mechanisms remain unclear, knowledge of the epidemiologic and virologic characteristics of AIDS is advancing rapidly and should lead to strategies for effective treatment and prevention.

The consequences of HIV infection upon the mucous membranes have been relatively unexplored despite much evidence of mucous membrane dysfunction in patients with AIDS. Mucous membranes may be viewed as lipid membranes whose epithelial cell intercellular junctions and cell surface membrane transport proteins confer an extremely selective permeability to soluble and particulate antigens. The mucous membranes face nonsterile environments but lack an

effective physical barrier such as skin. This feature of being the interface between the body and the external environment is common to all mucous membranes and is separate from the specialized transport functions, such as nutrient absorption in the small intestine and gas exchange in the lungs.

The defenses of the mucous membranes are highly specialized and use both immunologic and nonimmunologic factors. In the case of the gastrointestinal (GI) tract, the nonimmunologic factors include gastric acid secretion, antiinfective materials present in the endogenous secretions and intestinal peristalsis. Mucosal immunity resembles systemic immunity in the central role played by T lymphocytes, but several distinctions exist. Secretory immunoglobulins, mainly dimeric IgA, are specialized in containing secretory component, a glycoprotein that retards intraluminal digestion.[1] Secretory IgA acts at mucosal surfaces to promote antigen exclusion from the body. Secretory immune function relies upon T lymphocytes, including "switch cells" which promote the early differentiation of plasma cell precursors and are found in mucosal lymphoid follicles such as Peyer's patches.[2] The subsequent development of B cells as well as antibody synthesis and secretion by plasma cells is modulated by lamina propria T cells. T lymphocytes in the GI tract also serve functions that are identical to those found in other organs, including the mediation of classic cell-mediated hypersensitivity reactions and the modulation of macrophage function.

The induction of tolerance—that is, induced hyporesponsiveness to a systemically administered antigen—is an important property that appears to be limited to T lymphocytes originating in mucosal lymphoid follicles.[3] Hyporesponsiveness is associated with suppressor T lymphocytes that migrate to the spleen and probably other lymph nodes in response to antigen stimulation. At the same time, helper T lymphocytes enter the systemic circulation, but return eventually to the lamina propria. It should be noted that a loss of this suppressor mechanism as a result of immunodeficiency could lead to an *exaggerated* systemic response to antigen stimulation.

The limited information presently available indicates that mucosal immunity in patients with AIDS is impaired, as would be expected from a loss of helper T lymphocytes. A recent study showed decreased population densities of IgA-containing plasma cells from colonic and small intestinal mucosa from patients with AIDS, associated with decreased secretion of soluble IgA.[4] There is an obvious impairment in cell-mediated immune function in the GI tract as evidenced by local reactivation or dissemination (or both) of cytomegalovirus, herpes simplex virus and adenovirus.[5] Overwhelming clinical experience has indicated that patients with AIDS are especially prone to reactivation of latent pathogens, such as the herpesviruses, *Mycobacterium tuberculosis* and toxoplasmosis, among others. A more unusual consequence of T-lymphocyte dysfunction in the intestine and elsewhere is lymphoproliferation of B lymphocytes, related to prior transformation by the Epstein Barr virus (EBV) with or without other agents.[6] This problem is illustrated by the great frequency with which B-cell lymphomas occur, especially in the brain and GI tract.[7] Another consequence of lymphoproliferation related to EBV infection is lymphocytic interstitial pneumonia, which appears to be common in children with AIDS[8] but clearly can occur also in some adults with AIDS.[6]

Macrophage dysfunction occurs in the intestines as demonstrated by intestinal involvement in disseminated *Mycobacterium avium-intracellulare* infections and in recurrent bacteremia due to *Salmonella* species.[9,10] The possible effect of AIDS upon the ability of intestinal lymphocytes to mediate tolerance has not been studied. It is conceivable that loss of tolerance to bacterial antigens could result in "autoantibody" formation[11] due to cross-reacting antigens, as is postulated to occur in other diseases.[12]

The major clinical consequence of AIDS upon the GI tract is the occurrence of multiple enteric infections, as described in the thorough review by Rodgers and Kagnoff in this issue. The available literature is well reviewed and many helpful recommendations are given. It is notable that the authors were unable to find evidence for an increased incidence of enteric infection with *Entamoeba histolytica* or *Giardia lamblia* in patients with AIDS, though these two pathogens represent common diagnoses in homosexual men without AIDS who have diarrheal illnesses.[13] The portions dealing with treatment of the infections are, understandably, pessimistic in tone. It is difficult, however, to assess the role of therapy in the opportunistic infections described, as patients may have several infections simultaneously and controlled trials are in large part lacking. Specific treatments, such as 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG), for patients with disseminated cytomegalovirus infections[14] prolong survival (D. P. Kotler, unpublished data), while treatment of disseminated infection with *M avium-intracellulare* with the use of multidrug regimens (four or more drugs) also may be efficacious. Since these two serious infections often are found to coexist, at least in New York City, the potential benefit of treating only one of the infections would be diminished. Furthermore, treatment of enteric infections often is prolonged. Since the immune deficit in AIDS results in the reactivation of latent infections, it should be no surprise that long-term suppressive therapy is needed. In this disease, drugs are being used to compensate for the loss of immunologic surveillance.

Despite the thorough and generally excellent review, the authors still fall short in their chosen task of fully describing the GI manifestations of AIDS. Two potentially important aspects that bear discussion are the roles of malnutrition and of intestinal injury with altered permeability upon the development and progression of the immune deficiency. The available published information in these areas is extremely limited.

The development of malnutrition may have special significance in cases of AIDS as malnutrition has both specific and nonspecific detrimental effects upon immune function, which range from circumscribed lesions due to micronutrient deficiencies to generalized impairment in the proliferation of lymphoid tissues from severe protein depletion.[15] Intestinal damage as a result of immune deficiency could promote malnutrition and provide feedback to further impair immune function.

It is widely recognized that severe malnutrition occurs commonly in patients with AIDS. It is not as well appreciated that AIDS may act as a chronic debilitating disease.[16] Extreme tissue depletion involving more than one half of the premorbid lean body mass may be found at death (J. Wang, personal communication). The depletion of body cell mass is kwashiorkor-like and resembles a stressed state rather than simple starvation.[16] There is little doubt that death in many

patients occurs due to the ultimate exhaustion of metabolic resources with complete breakdown of the natural defenses of the body, rather than to the aggressiveness of an opportunistic infection. This is demonstrated by the frequent occurrence of Gram-negative bacteremias with common enteric organisms late in the disease[17] or in postmortem blood cultures.

The role of intestinal damage in promoting malnutrition is complex. The relationship between intestinal damage and immunologic function also is unclear. It is well recognized that intestinal injury during local infections may have an immunologic basis rather than being a direct effect of the pathogen itself. In a classic study, Ferguson and Jarrett demonstrated the absence of histopathologic damage during experimental nematode infection in T-cell-depleted rats.[18] Intestinal injury, no matter what the precise cause, will promote dysfunction, including nutrient malabsorption. Intestinal malabsorption is quite prevalent in AIDS, involves both carbohydrates and fats and may be detectable even in the absence of diarrhea.[19] Nutritional repletion even by an intravenous route, however, often is unsuccessful so that the precise role of the GI tract in the development and progression of the malnutrition is unclear. Furthermore, malnutrition affects the intestines disproportionately due to the high rate of protein synthesis in the gut,[20] so that some element of intestinal dysfunction may be a result of malnutrition.

Another important consequence of mucous membrane dysfunction in AIDS is altered intestinal permeability, a factor that has not been examined to date. Early epidemiologic studies suggested that repeated insults to the systemic immune system from multiple infections favored the development of AIDS.[21] More recent clinical experience has indicated that many patients have been celibate and infection-free for prolonged periods of time and yet still have progression of disease. As stated above, the lipid barrier in the mucous membranes should deter penetration of most soluble protein antigens. The barrier could be disrupted by many factors such as impaired secretory immunity associated with increased local and systemic absorption of luminal antigens.[22] In addition, cytolysis occurring as a result of viral or other infections as well as focal crypt epithelial cell degeneration (apoptosis) in the GI tract not associated with viral-induced cytopathy[19,23] would result in the development of large aqueous channels through which antigens could enter the body. The resulting immune stimulation in the lamina propria probably includes the localization and proliferation of T helper cells,[24] which could be a reservoir for local retrovirus production in the laminae propria of the mucous membranes. By promoting retrovirus production, mucous membrane dysfunction might fit the role of a "cofactor" in disease progression. Thus, the mucous membranes may play a role in AIDS that is more central to its pathogenesis than merely serving as target for multiple pathogens.

It must be emphasized that the detrimental effects of AIDS should be similar in all mucous membranes. Thus, subclinical or clinical dysfunction, with or without detectable infection, would be expected in the lungs, tracheobronchial tree, oropharynx, nasopharynx and hypopharynx, nasal mucosa, sinuses, conjunctivae, urethra and vaginal mucosa, in addition to the GI tract. The proper and effective therapy for patients with AIDS will have to address these problems in addition to finding agents that effectively inhibit retrovirus replication and suppress the specific opportunistic pathogens.

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AIDS Virus and the Brain

THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) first became manifest in the United States in 1981 with the appearance of opportunistic infections and Kaposi's sarcoma in homosexual young men. In the early years of the AIDS epidemic, numerous reports documented a variety of infectious and neoplastic complications of the syndrome, including many which described disorders of the central nervous system. By 1983 it had become apparent that a substantial

group of patients with AIDS had evidence of a progressive dementia with cognitive impairment, with cerebral atrophy on computed tomographic scan.[1] Some of these patients had disseminated infection of the brain by cytomegalovirus, but in many an opportunistic pathogen could not be found.

In 1984 convincing clinical and virological evidence was presented to implicate a retrovirus, now called human immunodeficiency virus (HIV), as the cause of the immune deficiency.[2] In light of this evidence, a reevaluation of what had come to be known as AIDS encephalopathy or AIDS dementia was begun. Concurrently, a progressive encephalopathy, characterized by cognitive defects and impaired brain growth, was described in children with AIDS, a group that had recently been recognized as being involved by the syndrome.[3] There was general agreement that both the dementia in adult patients and the progressive encephalopathy in children represented a new disorder which had not been seen previously, including in persons with immune deficiencies. The pathological substrate of this neurological disorder seemed elusive, and in both adults and children it was noted that neuropathologic changes were often mild when compared with the severity of the dementia. One unusual finding was of multinucleated giant cells within the brain of affected persons. Cells of this type had not been seen before within the human central nervous system, and they bore striking similarity to fused, syncytial cells which occur in lymphocyte cell lines infected with HIV in vitro, although it was obvious that the brain multinucleated cells were not lymphocytes.[4]

Involvement of the nervous system had long been recognized with animal retroviruses, especially those of the lentivirus subfamily, including visna virus in sheep and the arthritis-encephalitis virus of goats. The pathologic features of these lentiviral disorders differed, however, from those of AIDS dementia. Nevertheless, experimental evidence of involvement of the brain by HIV soon appeared, when HIV was transmitted to chimpanzees that were inoculated with brain tissue from adults and children with the disorder, with seroconversion (although no clinical evidence of disease) in the recipient animals.[5] Concurrently the HIV genome was identified in brain tissue of patients with AIDS encephalopathy by molecular hybridization techniques.[6] Soon thereafter in rapid succession the following occurred: HIV was isolated from cerebrospinal fluid and central nervous system tissue in patients infected with the virus,[7] HIV particles were discovered to be associated with the multinucleated giant cells on ultrastructural examination[8] and HIV genome and antigen were localized to both multinucleated cells and brain macrophages.[9] The tempo of these overlapping studies has been dizzying, and a great deal has been learned about involvement of the central nervous system by this virus in a remarkably short period. Indeed, the time has been so short that neuropathologists have not yet devised a satisfactory term for the disorder; my own preference is for "HIV encephalitis."

The clinicopathologic conference in this issue presents a typical case of an adult with AIDS dementia. The brief clinical summary clearly indicates that the patient had AIDS complicated by a dementing disorder, as did one of his sexual partners who had died of AIDS. At postmortem examination, the presence of HIV was not conclusively demonstrated within the tissue, either by isolation or by any other method, yet the pathologic changes (microglial nodule encephalitis with multinucleated giant cells) were characteristic of brain involvement by the virus. As is frequently the case in adult AIDS patients coming to autopsy, this pathologic picture was complicated by other disorders, the most prominent of which was cytomegaloviral encephalitis. The case is similar to several of those of Navia and co-workers,[10] with combined features of HIV and cytomegalovirus involvement. It is also straightforward in that the patient had already had AIDS, with *Pneumocystis carinii* pneumonia, before the onset of dementia. The case reported by Mirra and colleagues[11] is more disquieting because that patient's dementia presented without evidence of immune deficiency, leading to an erroneous clinical diagnosis of Alzheimer's disease; at autopsy multinucleated giant cell encephalitis was found, prompting postmortem confirmation of HIV infection of the brain.

As Vinters's discussion indicates, however, not all the answers are in. The chief gap in our current understanding of the role of HIV in the pathogenesis of AIDS dementia is the lack of convincing evidence of neurotropism of this virus. A neurotropic virus is one that is capable of infecting cells of neuroectodermal origin, chiefly neurons (as is seen with such viruses as poliomyelitis virus or herpes simplex virus type I) or glial cells (as occurs in progressive multifocal leukoencephalopathy, in which a papovavirus infects oligodendroglial cells) or both. In addition to the macrophage and multinucleated cells, only brain endothelial cells have been found to harbor HIV.[9] It is unclear how infection of inflammatory or endothelial cells alone can produce the clinical dementia. Neuronal loss does not seem to be a major feature of this disorder, although neuron counts have not been done. On the other hand, there does appear to be some effect in the white matter because diffusely diminished myelin and white matter gliosis are frequently seen in brains from these patients. Several pathogenetic mechanisms are possible. The virus might cause a direct, as yet undetected, effect on the myelin supporting cells, or perhaps the infected inflammatory cells might release a substance that is toxic to these or other cells. A viral protein could function as a false neurotransmitter, perturbing nervous system function without producing further morphologic damage. It is also possible that HIV proviral DNA might incorporate itself into the genome of neurons or glial cells and alter cellular function without producing any recognizable cytopathic effect. Alternatively, another agent, as yet unrecognized, might act, either alone or in concert with HIV, to produce the observed neurological dysfunction, a notion that is not farfetched, given the multiplicity of opportunistic pathogens reported in the nervous system of patients with AIDS. Further research is urgently needed to elucidate this problem.

An obstacle to progress has been the failure to produce significant clinical disease, either immunologic or neurologic, in any animal inoculated with HIV. The endangered chimpanzee *(Pan troglodytes)* is the only species which is capable of being infected by the virus, and those chimpanzees which have been infected have so far shown no significant abnormalities. Nevertheless, an animal model has emerged, almost providentially. At the same time that the human virus was being characterized, a related retrovirus, termed simian T-lymphotropic virus type III (STLV-III), was discovered in nonhuman primates, initially in rhesus monkeys *(Macaca mulatta)*, with other strains more recently isolated from other

species.[12] Some of the strains of STLV-III, when inoculated into juvenile rhesus monkeys, have produced clinical AIDS and neurological deterioration that are remarkably similar to that seen in humans with HIV infection, including the presence of multinucleated giant cells in brain tissue.[13,14] These are exciting findings because, from the molecular biologic standpoint, HIV is more closely related to STLV-III than to any other human or animal retrovirus.[15] Such aspects of HIV involvement of the brain as entrance of the virus into the central nervous system and cerebrospinal fluid, pathogenesis of the encephalopathy and persistence of the virus can be more readily addressed with the STLV-III model than with infection in humans.

The most practical aspect of involvement of the brain by HIV, regardless of the pathogenesis of the dementing disorder, concerns potential treatment of patients infected with the virus. Recent evidence suggests that the virus enters the central nervous system in most, if not all, patients infected with HIV, in some cases quite early after the initial infection.[16] Current treatment protocols have recognized that the central nervous system can be a sanctuary for the virus, and several agents have been dismissed because they do not cross the blood-brain barrier. Azidothymidine, an agent which has been shown to slow progression of the immune deficiency in preliminary trials,[17] does, however, cross into the cerebrospinal fluid. It is possible that reconstitution of a damaged immune system in a person whose brain has been invaded by HIV may trigger a more vigorous inflammatory response directed against the virus, thereby resulting in secondary damage to the brain, although evidence for this has not yet been reported. As with so many facets of the AIDS epidemic, involvement of the brain by the AIDS retrovirus is one more problem which is not going to go away quickly.

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Case Reports

Psittacosis

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HUMAN PSITTACOSIS is a respiratory or systemic illness caused by infection with *Chlamydia psittaci*. It is contracted by being exposed to discharges of infected birds; therefore, it is a zoonosis. The disease is called psittacosis if acquired from psittacine birds (parrots, parakeets and related species) and ornithosis if acquired from nonpsittacine birds (chickens, pigeons, pheasants, turkeys, ducks). It may rarely be contracted from nonavian sources such as cattle, sheep, cats or other humans. The disease has also been reported in laboratory personnel working with chlamydiae. If recognized early and treated appropriately with tetracycline, the disease generally has little morbidity and low mortality. Failure to consider the diagnosis, however, may result in prolonged illness, serious sequelae and a higher mortality.

Two recent cases of typical psittacosis underscore the importance of obtaining an epidemiologic history, more specifically, a history of exposure to birds or other vectors, in patients presenting with fever and pulmonary infiltration.

Reports of Cases

Case 1

The patient, a 35-year-old male lithographer, was admitted to hospital for treatment of left lower lobe pneumonia in May 1985. Nine months before admission, left pleuritic chest pain without fever developed and continued for three or four days. A chest roentgenogram showed a left pleural effusion, and there was a mild leukocytosis (11,700 per μl). Findings of thoracentesis were a yellow fluid, pH 8.1, a protein level of 5.2 grams per dl and glucose 96 mg per dl. The leukocyte results were lost. Levels of lactic dehydrogenase (LDH) from pleural fluid and serum specimens were 162 and 85 IU per liter, respectively. The patient was treated with a ten-day course of erythromycin, 250 mg four times a day, and sent home. A purified protein derivative (PPD) skin test (5 tuberculin units) was negative at 48 hours; a skin test for mumps was positive. Cultures of pleural fluid specimens for bacteria, fungus and acid-fast bacilli were negative, and cytologic studies showed only reactive mesothelial cells. Ten days later the patient felt well and results of a physical examination were entirely normal.

Six days before admission, a persistent fever to 40.5°C (104.9°F) developed, and he had delirium, shaking chills, generalized myalgias and malaise. Two days later he had a cough productive of scanty, thick yellow sputum, substernal chest pain, headache and anorexia. He had no photophobia, neck stiffness, adenopathy, rash, arthralgia, diarrhea or dysuria.

The next day he had a fever to 39.1°C (102.4°F) and coarse breath sounds at both bases. A 0.3-cm nodule in the left axilla was thought to be a skin abscess and was incised and drained. The leukocyte count was 9,500 per μl with a left shift, and a chest roentgenogram was normal. The examining physician thought he had a viral syndrome, prescribed acetaminophen and sent him home. Nausea, emesis and crampy abdominal pain occurred during the hours before hospital admission.

The patient was single, heterosexual and lived in a rooming house in San Francisco. He did not smoke cigarettes or use alcohol or intravenous drugs. Three months before his illness, he had killed and skinned two rabbits. His landlady's two pet cockatiels (apparently domestic) had died the same month (May) of unknown causes, and his cat had had a recent gastrointestinal illness.

On physical examination, he was acutely ill, in a mildly toxic condition and somewhat anxious. The temperature was 39.1°C, the pulse rate 120 beats per minute, respirations 12 per minute and unlabored and blood pressure 110/70 mm of mercury. There was a small, erythematous macule in the left axilla (at the site of prior incision and drainage). The pharynx was injected but without exudate. A small, tender left axillary node was palpable. The neck was supple, and there were coarse rales at the left posterior base with egophony and bronchial breath sounds. The heart had a tachycardic, regular rhythm and summation gallop, but no murmur. There was mild right upper quadrant tenderness, but no hepatomegaly, and one observer noted a palpable spleen tip. Findings of a neurologic examination were nonfocal.

The results of a complete blood count and serum chemistry tests were normal, except for a serum sodium level of 130 mEq per liter; the erythrocyte sedimentation rate was 50 mm per hour, and analysis of urine showed a specific gravity of 1.024, 2+ protein and 1+ ketones. A chest x-ray film showed a left lower lobe infiltrate and blunted left costophrenic angle consistent with a small pleural effusion (Figure 1). Gram's stain of a sputum specimen showed moderate polymorphonuclear leukocytes and scattered Gram-positive cocci. Cultures of sputum, blood and urine were negative for pathogens, and serum specimens were taken for serology. The rapid plasma reagin test for syphilis

(McPhee SJ, Erb B, Harrington W: Psittacosis. West J Med 1987 Jan; 146:91-96)

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ABBREVIATIONS USED IN TEXT

ALT = serum alanine aminotransferase
AST = serum aspartate aminotransferase
Ig = immunoglobulin
LDH = lactic dehydrogenase
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure
PPD = purified protein derivative

was nonreactive, and the titer for tularensis agglutinins was less than 20. The patient was initially treated with tetracycline, 500 mg four times a day; erythromycin, 500 mg four times a day, was added when his temperature rose to 40.3°C (104.5°F).

His condition gradually improved, with the fever and cough resolving over the next several days. Following discharge, convalescent serum specimens were obtained. Acute and convalescent complement fixation antibody titers for *Chlamydia* confirmed the diagnosis of psittacosis, with a fourfold rise from 1:8 on May 21, 1985, to 1:32 on June 3, 1985. There was no change in complement fixation antibody titers for influenza A or B, adenovirus, *Mycoplasma* or Q fever. A month later he was entirely well.

Comment. This man had typical pneumonitis and systemic features of the acute form of psittacosis. The occurrence of acute pneumonitis and splenomegaly suggests the diagnosis. Although the culture-negative pleural effusion nine months before admission might have also been due to *C psittaci* (because antibodies are not protective), the initial complement fixation titer was probably too low for this possibility. The history of exposure to rabbits suggested the diagnosis of pleuropulmonary tularemia, but exposure occurred three months before the illness, making it unlikely. Although *C psittaci* infection may be acquired from cats (and the patient's cat had been ill), the patient's infection was most probably acquired from one of the two pet cockatiels that had been purchased recently.

Figure 1.—A lateral chest radiograph of the patient in case 1 shows a consolidation of moderate size in the left lower lobe and a small left pleural effusion.

Case 2

The patient, a 35-year-old licensed vocational nurse, had been in excellent health until September 1982, when she noted fatigue and both her hands were cold. The next day she noted malaise and had a fever to 38.8°C (101.8°F), lightheadedness, nausea and mild right upper quadrant and midepigastric abdominal pain; the following day anorexia and mild frontal headache occurred. On the third day her temperature increased to 39.5°C (103.1°F) and rigors developed. On physical examination the following day, she had a temperature of 38.8°C, mild right upper quadrant tenderness and an epigastric bruit. Serum chemistry tests showed mild elevations of serum aspartate aminotransferase (AST, formerly SGOT) and serum alanine aminotransferase (ALT, formerly SGPT) levels, with a normal serum alkaline phosphatase value. A Monospot slide test for infectious mononucleosis was negative. She was told she probably had viral hepatitis and was sent home. Her fever was not suppressed by taking aspirin.

The following day, increasing malaise and a persistent, nonproductive cough developed. Her temperature ranged between 39.5°C and 40°C (104°F), and her physician noted rales in the left lower lung. A chest x-ray film showed right upper and lower lobe infiltrates. Results of a complete blood count were normal; the erythrocyte sedimentation rate was 85 mm per hour. Cold agglutinins were absent. Serum chemistries showed an AST level of 28 and an ALT value of 70 IU per liter. Arterial blood gas determinations made while the patient was breathing room air showed a pH of 7.51, a partial oxygen pressure (P_{O_2}) of 65 torr and a partial carbon dioxide pressure (P_{CO_2}) of 20 torr. Cultures of sputum, blood and urine specimens were negative for pathogens. Ultrasound examination of the abdomen was unrevealing. She was treated with nafcillin sodium and tobramycin given intravenously, but her condition did not improve. One week after the onset of symptoms, fever persisted and she had increasing dyspnea. Arterial blood gas measurements with the patient breathing room air showed pH 7.51, P_{CO_2} 20 torr and P_{O_2} 64 torr.

She had been previously well except for mild hypertension—treated only with dietary sodium restriction—and a history of hyperthyroidism with exophthalmos, treated with antithyroid medications. A PPD skin test had been positive one year previously; the chest roentgenogram had been normal and no therapy had been prescribed.

On physical examination on admission, she appeared moderately ill and had dyspnea. The temperature was 39.5°C, the pulse rate 130 per minute, the respirations 24

per minute and the blood pressure 105/75 mm of mercury. There were a few urticarial lesions on the thighs and knees. The conjunctivae were injected, the neck was supple and there was no adenopathy. Chest examination showed dullness and decreased breath sounds at both bases posteriorly, and there were coarse rales and bronchial breath sounds over the entire left and lower right lung fields posteriorly. There was a grade 2/6 systolic ejection murmur. There was mild right upper quadrant and epigastric tenderness; the hepatic span was 8 cm to percussion. The spleen was not palpable. An epigastric bruit was again noted. A stool specimen was positive by guaiac test. The remainder of the examination showed no abnormalities.

Results of a complete blood count, differential and serum chemistry tests were normal, except for elevated values for liver function tests (serum alkaline phosphatase 130 IU per liter, AST 46 IU per liter and LDH 182 IU per liter). A urinalysis showed 1+ protein, trace heme, 5 to 10 leukocytes and 5 to 10 erythrocytes per high-power field. A chest roentgenogram showed right upper and bilateral lower lobe infiltrates and bilateral small pleural effusions (Figure 2). Results of arterial blood gas analyses with the patient receiving five liters of oxygen per minute by nasal prongs showed pH 7.51, Po_2 76 torr and Pco_2 25 torr. Gram's stain and acid-fast smear of sputum specimens were negative for pathogens. Cold agglutinins were absent. Cultures of sputum, blood, urine, cervical and stool specimens were negative. A coccidioidomycosis counterimmunoelectrophoresis test was negative, and *Legionella* and *Mycoplasma* complement fixation antibody titers were done and subsequently were negative. The patient was initially treated with a regimen of nafcillin sodium, tobramycin and erythromycin.

The following day, it was learned that one month before admission the patient's husband had brought home a pet cockatiel from a private aviary in El Sobrante, California. About two weeks later, the bird had become ill with lethargy and rhinitis and was given chlortetracycline hydrochloride (Aureomycin) for five days. The patient became ill toward the end of the bird's antibiotic therapy.

Subsequent serologic studies showed the following microimmunofluorescence antibody titers: anti-*Chlamydia psittaci* immunoglobulin (Ig)G 1:128, anti-*C psittaci* IgM 1:128, anti-*Chlamydia trachomatis* IgG 1:32 and anti-*C trachomatis* IgM 1:32. The antichlamydial antibody complement fixation titer was 1:16.

The patient was thereafter treated with tetracycline, 500 mg four times a day. Her condition improved rapidly over the next several days, with resolution of the chest abnormalities and improvement of the arterial blood gas values to pH 7.46, Pco_2 33 torr and Po_2 80 torr with the patient breathing room air. She was discharged on the sixth hospital day and an additional 18-day regimen of tetracycline was prescribed. A similar respiratory illness had developed in the patient's 9-year-old daughter, who was also treated with a tetracycline regimen. Her cockatiel was given Keet Life (chlortetracycline) for 45 days. The State Department of Public Health was contacted and the aviary placed under quarantine until further investigations were conducted.

Comment. Both severe multilobar pneumonia with hypoxemia and mild nonspecific hepatitis from psittacosis developed in this woman. She became progressively ill despite treatment with broad-spectrum antibiotics until the history of bird exposure was elicited, the diagnosis of psittacosis considered and tetracycline therapy begun. Her daughter probably also had a mild case of psittacosis from

Figure 2.—Left, Posteroanterior and **right,** lateral chest radiographs from case 2, showing patchy consolidation in both lower lobes, focal nodular density in the right upper lobe and small bilateral pleural effusions.

exposure to the household source. Appropriate measures were taken to ensure eradication of the infection both in the patient's home and at the aviary.

History

The history of psittacosis is only a century old. Jurgensen may have been the first to describe the typical pneumonia of psittacosis. Ritter recognized the first outbreak of human psittacosis in 1879 in Ulster, Switzerland. Seven cases of fever, pneumonia and stupor followed in people exposed to sick birds, and three proved fatal.[1] Following 4 cases (2 fatal) in 1882 in Bern, Switzerland, and 47 cases (13 fatal) in Paris in 1892, Morange in 1895 coined the term "psittacosis" from the Greek *psittakos* (parrot). An epidemic, however, in 1929-1930 of 750 to 800 cases originating in Argentina and affecting the United States, Europe and Africa led to the discovery of the responsible agent. In 1930 Krumweide and Armstrong in the United States, Levinthal in Germany and Bedson in the United Kingdom discovered the responsible organism. Levinthal, Coles (United Kingdom) and Lillie (United States) described coccobacillary forms seen under light microscopy, subsequently known as Levinthal-Coles-Lillie bodies. Also in 1930, according to Schachter and Dawson, Bedson and Western devised the complement fixation antibody test that has remained the mainstay of diagnosis.[2]

Microbiology

Chlamydia psittaci (responsible for psittacosis) can be readily distinguished from *Chlamydia trachomatis* (differing serotypes of which are responsible for lymphogranuloma venereum, trachoma, inclusion conjunctivitis, nongonococcal urethritis, cervicitis, salpingitis, proctitis, epididymitis and pneumonitis of newborns) by its lack of cell-wall staining with iodine. It can be grown in mice, in chick egg embryos and in a variety of cell cultures. Chlamydiae are obligate intracellular microorganisms, more similar to bacteria than viruses in that they are sensitive to some antibiotics, contain both DNA and RNA and have discrete cell walls, resembling those of Gram-negative bacteria. Because they cannot synthesize adenosine triphosphate and require other metabolites for growth, they must live within cells. When they infect the host cell, they take over its synthetic processes and direct them toward producing more chlamydiae.[3-5]

The developmental cycle of chlamydiae is complex, lasting about 48 hours. The 350-nm elementary body is the infectious particle, capable of attaching to the surface of susceptible host cells, such as epithelial cells of the respiratory tract, and of inducing its own phagocytosis. Once inside the cell, the elementary body reorganizes within six to eight hours to form the 800-nm metabolically active initial (reticulate) body. The initial body then synthesizes new materials and divides repeatedly by binary fission. Some 18 to 24 hours after infection, the initial body then stops multiplying, reorganizes and condenses to form the elementary body, which is capable of survival in the extracellular environment. In the cell environment, chlamydiae live in phagosomes throughout their developmental cycle. They are able to prevent phagosomes from fusing with lysozomes until very late in the cycle.[3-5]

Clinical Manifestations

Psittacosis is rare in children younger than 10 years; it is more severe in adults older than age 40.[6] The incubation period varies from 7 to 15 to as much as 30 to 39 days, the shorter incubation periods resulting from heavier exposure.[2]

Presentations vary considerably with a predominance of respiratory tract symptoms (nonproductive cough, dyspnea, pleurisy, epistaxis, sore throat and, rarely, hemoptysis) and systemic symptoms (fever, malaise, rigors, sweats, headache, anorexia, nausea and vomiting and abdominal pain). Less common are photophobia, conjunctival suffusion, generalized arthralgias, myalgias, stomach cramps and diarrhea. Physical signs include fever, rales, pulmonary consolidation, pharyngeal erythema, hepatomegaly, altered mental state, pleural friction rub, slow pulse rate relative to temperature and splenomegaly.[6] Rales or rhonchi are detected in about a fifth of patients, but the majority have roentgenographic evidence of pneumonia. Relative bradycardia is noted in about a third of patients.[7-12]

Unusual manifestations of psittacosis include erythema nodosum, pericarditis and pericardial effusion, myocarditis and congestive heart failure, hepatic granulomata, myositis, rhabdomyolysis, reactive arthritis, encephalitis, abortion and hemolytic anemia.[13-25] In addition, there have been several recent reports of culture-negative infective endocarditis caused by *C psittaci*. The clinical presentation has generally been one of subacute endocarditis of the mitral or aortic valve, some cases failing to respond to prolonged tetracycline therapy and requiring valve replacement.[26-32]

Pathology

In birds the primary sites of disease are the liver, spleen and pericardium; in humans the lung is most often involved.[5,6] The pulmonary lesion is a lobular interstitial pneumonitis, extending from hilum to periphery, typically of dependent lobes and segments. There may also be severe tracheobronchitis. The spleen shows gross and microscopic findings of acute splenic tumor; the liver, nonspecific hepatitis; the heart, interstitial myocarditis, edema and subendocardial hemorrhage, and the brain, lymphocytic meningitis and arachnoiditis.

Epidemiology

Psittacosis is a reportable disease. In 1979 there were reported 116 cases of confirmed or presumptive psittacosis and 1 death in 25 states. Most cases were reported in the West, with California accounting for 27 (23%).[33]

Although bird bites may occasionally result in disease, humans usually acquire psittacosis by inhaling *C psittaci* organisms, which are present in exudates of birds with serous conjunctivitis or purulent rhinitis, in dried excrement in the environment and in organs and feathers of infected birds. In the poultry industry, the greatest risk is for workers who pluck and eviscerate turkeys.[9,11] Exposure to the source of infection must not be prolonged or intense; cases have resulted from brief visits to rooms where there were infected birds.[10] Latent or inapparent infection in apparently healthy birds (who nonetheless shed chlamydiae in their excrement) may represent low levels of multiplication held in check by host defenses.[5] In addition, human-to-human transmission

and transmission by other animals, including cattle, sheep and cats may rarely occur.[34,35] A carrier state for *C psittaci* was reported by Meyer and Eddie in 1951.[36]

Differential Diagnosis

The differential diagnosis of psittacosis is that of atypical pneumonia. It includes both relatively common illnesses, such as *Mycoplasma pneumoniae,* Legionnaire's disease and the viral pneumonias (influenza, parainfluenza, adenovirus, varicella, cytomegalovirus and respiratory syncytial virus) and uncommon causes of atypical pneumonia, such as Q fever, pleuropulmonary tularemia and *Pneumocystis carinii* pneumonia. Tuberculosis, atypical mycobacterial infection and fungal infection (especially histoplasmosis and coccidioidomycosis) must also be considered.

The best clues to the correct diagnosis of psittacosis are a history of exposure to birds in a person with a flulike illness or a chest roentgenogram that shows pulmonary infiltrates far more extensive than the symptoms or physical findings would suggest.[12]

Diagnosis

All chlamydiae share the same complement-fixing antigen. Thus, the widely used complement fixation test does not distinguish between *C psittaci* and *C trachomatis.* The clinical syndromes caused by each, however, are sufficiently different for this to be a minor problem.

Antibodies usually appear in the second to fourth week of illness, but early and prolonged treatment with tetracycline may delay, decrease or suppress antibody production, making serologic diagnosis difficult. Diagnosis may be aided by comparing complement fixation antibody titers early in the illness, throughout the convalescence and several months later; alternatively, a physician may be aided by obtaining blood or sputum specimens for isolation of chlamydiae before beginning antibiotic treatment.[37]

The complement fixation test is useful in diagnosis if appropriately timed (acute and convalescent) serum specimens show rising antibody titers. Seroconversion is defined as an increase of fourfold or greater, or a titer of less than 1:8 rising to more than 1:16. If a specimen is not obtained during the acute phase, single titers of 1:64 to 1:256 or more support the diagnosis. Although isolation techniques are no longer particularly difficult, the risk of infection to laboratory workers is great enough to advise that it be attempted only in specially equipped laboratories.[2]

The Centers for Disease Control define a confirmed case as a clinical specimen positive for *C psittaci* or an illness characterized by any combination of fever, chills, lower or upper respiratory tract disease, myalgias, headache, photophobia and splenomegaly plus a fourfold or greater rise in complement fixation antibody titer to 1:32 or more on two serum specimens obtained two or more weeks apart and studied in the same laboratory. A presumptive case is defined as a compatible illness and either an antibody titer of 1:32 or more on a single specimen or a stable titer of 1:32 or greater on two or more serum specimens.[33]

Newer diagnostic tests that distinguish between the two species, such as enzyme-linked immunosorbent assays and monoclonal antibody techniques, are now being evaluated.[38]

Morbidity and Mortality

Host defenses against chlamydiae may involve both cell-mediated and T-cell-dependent humoral immune responses. Humans show no prolonged immunity, and relapses or reinfections have been reported even for persons with high complement fixation antibody titers.[7]

Before antibiotics, the untreated disease usually lasted two to three weeks, but fever and illness sometimes persisted for two months or longer. Convalescence was prolonged and relapses occurred.

Mortality was 10% to 40% in the preantibiotic era.[10] Today, estimated mortality ranges from 1% to 5% (but, if the disease is recognized early and treated appropriately, mortality can be as low as 0.5%).[9] About a fourth of patients in recent epidemics have required hospital admission for 4 to 16 days.[11]

Prevention and Treatment

Chlortetracycline-impregnated birdseed and quarantine programs for imported birds have been used in an attempt to reduce the spread of the disease.[2] A study by Schachter and colleagues, however, shows that, despite such measures, the reservoir of infection persists. During a one-year period, they tested tissue specimens from 101 ill or dying parakeets and parrots in the United States for *C psittaci*; 37 (37%) were positive.[39]

Experimental efforts to immunize humans against psittacosis have been disappointing.[3]

The treatment of choice for psittacosis is tetracycline, 2 to 3 grams given in divided doses daily. Erythromycin is suggested as an alternative in children and pregnant women or in adults allergic to tetracycline, but may not be as effective. Experience with other antibiotics (chloramphenicol and rifampin) is limited.[2,10] To prevent relapses, therapy with tetracycline should be prolonged (anecdotal evidence suggests three weeks).

Defervescence after therapy is instituted may occur within one to six days.[12] A dramatic response to tetracycline, with the temperature dropping from 40.6°C (105.0°F) to normal within four hours has been reported.[40] In some cases, however, defervescence may be quite slow. The use of acetaminophen should probably be avoided because it may accentuate the hepatitis produced by psittacosis; such a reaction may prove fatal.[41]

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Nine Episodes of Infective Endocarditis in One Patient—A New Record

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INFECTIVE ENDOCARDITIS is a frequent complication of intravenous drug abuse, and recurrence is common if parenteral drug abuse continues.[1-3] Right-sided endocarditis in drug abusers has a mortality rate of 5% to 15%, while the mortality for each episode of left-sided endocarditis is 24% to 64%.[3-5] The likelihood of surviving several episodes of left-sided bacterial endocarditis is therefore small, and previous publications have reported no more than six episodes in a single patient.[6] We report the case of a patient who has survived nine documented episodes of mitral valve infective endocarditis over a 12-year period, including two episodes of fungal endocarditis and two mitral valve replacements.

Report of a Case

The patient is a 34-year-old man with a history of intravenous drug abuse since 1967. His first episode of mitral valve endocarditis was diagnosed in October 1972, when he came to San Francisco General Hospital Medical Center (SFGHMC) with fever and a murmur of mitral regurgitation. Multiple cultures of blood specimens grew group D *Streptococcus*. The patient was treated with a regimen of penicillin G and streptomycin sulfate given intravenously for 30 days and recovered without complication. He continued to use intravenous drugs and had eight subsequent episodes of endocarditis over the next 12 years (Table 1), all treated at SFGHMC. At least four of these episodes were complicated by congestive heart failure. Two episodes (numbers 5 and 6) were caused by persistent *Candida* infection complicated by bacterial superinfection. There was never any evidence of right-sided valve infection. In 1978 he underwent mitral valve replacement for persistent fungal endocarditis, and the two subsequent bacterial infections were cured medically, despite this prosthesis. In July 1984 he was diagnosed as having combined bacterial and fungal endocarditis and was given another mitral valve replacement (despite objections from some consultants) in conjunction with antimicrobial therapy. During the operation he was found to have abscesses in the mitral annulus. At last follow-up (November 1986), the patient was mildly disabled and receiving medical therapy for New York Heart Association class II congestive heart failure. He had no signs of infection and said he had discontinued intravenous drug use. Blood specimens drawn in November 1986 and cultured for bacterial and fungal pathogens were sterile.

Discussion

Recurrent infective endocarditis has been defined as a new intracardiac infection developing either more than six months after cure of an initial infection, regardless of pathogen, or by infection with a new organism regardless of time elapsed.[3,7] The remarkable case of the patient reported here met the first criterion in episodes 3 and 7, the second in episodes 4 and 5 and both criteria in episodes 2, 6, 8 and 9 (Table 1).

Recurrences of infective endocarditis are common in parenteral drug abusers. One study found that second episodes occurred in 17% to 24% of patients, and 5% had third episodes within a mean follow-up time of 20 months.[5] These rates are much higher than the 4% to 8% reinfection rate seen in the nonaddict population.[7] In 1979 Mokotoff and co-

workers reported the case of a drug abuser who had six episodes of left-sided bacterial endocarditis and an aortic valve replacement; the patient died during the sixth infection.[6] In reviews of published studies and discussions with authorities in this field, we have learned of no more than six episodes of infective endocarditis occurring in a single patient.[6]

Mortality figures for the first occurrence of right-sided infective endocarditis range from 5% to 15% and for left-sided infection from 24% to 64%.[3-5] Welton and colleagues found that if debilitated patients were excluded from a study of patients with one or two recurrences—that is, two to three total episodes—of either right- or left-sided infective endocarditis, the mortality increased from 9% with the initial episode to 25% for subsequent episodes.[3] Disease in the left side of the heart was present in 85% of those who died of recurrent endocarditis and the mortality for recurrent left-sided endocarditis was 35%.[3] Hubbell and associates found a mortality range of 24% to 33% with mitral valve endocarditis and a mortality of 33% with second or third episodes of endocarditis.[5] The presence of heart failure greatly increases the risk of death from endocarditis.[2,3,5,8] In one study, the one-year mortality of patients with endocarditis complicated by mitral insufficiency and severe heart failure was 80%, whereas in patients with endocarditis complicated by mitral insufficiency but with absent or mild heart failure, the one-year mortality was 20%.[8] In fungal endocarditis the mortality approaches 80% despite aggressive management with a combination of antifungal agents, surgical debridement and valve replacement.[9-11] Therefore, the calculated likelihood of this patient surviving the infections and procedures documented in Table 1 is between 0.05% and 0.5%, a remarkable tribute to his physical resilience.

Beneath the extreme statistics of this case lie a number of troublesome ethical and economic issues. A study of survivors of valve replacement for endocarditis found that in all three patients with a history of intravenous drug abuse, recurrent infection developed on the prosthesis, versus none of eight patients who lacked a history of intravenous drug abuse ($P = .006$).[3] Hubbell and co-workers described the cases of 25 intravenous drug abusers who had received prosthetic valve replacement for endocarditis. In this group, second infections developed in 24% and only 32% lived beyond the mean of 16 months' follow-up.[5] The high rate of failure caused by recurrent infection in patients who are intravenous drug abusers makes valve replacement in these patients of dubious long-term value.

The patient reported here has been in hospital for more than one full year out of the past twelve for treatment of endocarditis; this figure does not include known hospital admissions for other problems largely related to drug abuse. Today the average daily cost for an inpatient stay at SFGHMC is more than $500; the cost of mitral valve replacement is about $20,000. At today's prices we estimate that this patient has received almost a quarter of a million dollars of health care. In the past our society has not placed fiscal or other restraints on the availability of health care to persons with

TABLE 1.—*Microbiologic Features of Episodes of Endocarditis*

Episode, Number	*Date of Presentation*	*Infective Organism*	*Treatment*	*Length of Hospital Stay, Days*
1	October 1972	Group D streptococci	Penicillin G, streptomycin sulfate	30
2	January 1976	Viridans streptococcus; antimicrobial resistance—none*	Ampicillin, streptomycin sulfate	33
3	Nov 10, 1976	Viridans streptococcus; antimicrobial resistance—methicillin, tetracycline, kanamycin*	Penicillin G, gentamicin sulfate	10†
4	Nov 25, 1976	*Candida parapsilosis*	Amphotericin B	82
5	May 1977	*Staphylococcus aureus* *Candida parapsilosis*	Methicillin sodium, rifampin, amphotericin B	73
6	December 1977	Viridans streptococcus, *Candida parapsilosis*	Penicillin G, streptomycin sulfate, rifampin, amphotericin B, mitral valve replacement	64
7	May 1980	Viridans streptococcus	Penicillin G, streptomycin sulfate	13†
8	September 1982	*Streptococcus faecalis*	Penicillin G, streptomycin sulfate	41
9	July 1984	Viridans streptococcus, *Candida parapsilosis*	Penicillin G, nafcillin sodium, gentamicin sulfate, ketoconazole, amphotericin B, mitral valve replacement	29
			Total Hospital Days	375

*Tested by disc diffusion.
†Left hospital against medical advice.

problems of recurrent self-abuse. Given the increasing sophistication and cost of medical technology and the decreasing resources available for medical care, it is not clear that this attitude of infinite charity can be supported in the future.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Use of Botulinum Toxin

To the Editor: In the Correspondence section of the October issue, Nancy M. Newman, MD, wrote regarding the use of botulism toxin as an alternative therapy for hemifacial spasm.[1]

It is my understanding that this botulism titer is no longer available because the company that was producing it was unwilling to accept the potential liabilities associated with the production of the toxin. I would appreciate receiving any information you may have in regard to the availability of this potentially useful drug.

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REFERENCE

1. Newman NM: Chemical Denervation for hemifacial spasm (Correspondence). West J Med 1986 Oct; 145:520

* * *

To the Editor: In her letter,[1] Dr Newman is quite correct in pointing out that small doses of botulinum toxin can be used to successfully treat some patients with essential blepharospasm.

This form of treatment has not been recommended, however, for hemifacial spasm. Hemifacial spasm is considered to be an entirely different clinical entity. Chemical denervation of the entire facial musculature, to my knowledge, is not being done.

I would hope that you would make this correction in the Correspondence section of the journal so that others might not consider the use of botulinum toxin appropriate for hemifacial spasm.

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REFERENCE

1. Newman NM: Chemical Denervation for hemifacial spasm (Correspondence). West J Med 1986 Oct; 145:520

* * *

Dr Newman Responds

To the Editor: Dr Hayes asks for information about the availability of botulinum toxin. For a time it was not available because of difficulties with obtaining liability insurance. There was no problem with the producing company "being uncomfortable with the potential liabilities." It is available now, with the insurance problems having been solved.

In response to Dr Benecke's comments, hemifacial spasm has been quite successfully treated by a number of investigators over the last several years.[1]

Dr Benecke is correct that chemical denervation of the entire facial musculature is not done; however, the orbicularis is treated as in blepharospasm and additional injections in the mid-face, around the mouth, and the chin, can achieve a quite normal face with very little extraneous movement without functional weakness and drooling.

I have personally used this treatment in patients who have previously had one and two unsuccessful posterior fossa procedures for decompression of the VIIth nerve, as well as in patients who have not previously had operations.

As mentioned in my original letter, chemodenervation currently has the disadvantage of needing to be repeated; however, I believe this to be an important alternative to surgical procedures currently available and, frequently, the only highly effective treatment available to those patients who have had failed surgical procedures.

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REFERENCE

1. Savino PJ, Sergott RC, Bosley TM, et al: Hemifacial spasm treated with botulinum A toxin injection. Arch Ophthalmol 1985 Sep; 103:1305-1306

Nonindigents in the AHCCCS Plan

To the Editor: The correction in the September issue[1] by Jane Orient, MD, to her article on the Arizona Health Care Cost Containment System (AHCCCS) in the July issue[2] was correct, until she attempted to interpret it.

In her correction, Dr Orient said, " 'The inclusion of indigents has not occurred' should read 'The inclusion of nonindigents has not occurred.' " That correction was absolutely proper. She then, however, added, "Or perhaps better, 'nonindigents have not elected to join any of the plans.' " That statement is absolutely incorrect.

AHCCCS regulates the prepaid health plans with which it contracts and has not yet authorized them to market to the private sector. In short, nonindigents cannot join any AHCCCS plan because the plans are not permitted to accept them. One of those plans has formed a separate corporation regulated by the State Department of Insurance to offer coverage in the private sector. It now has an estimated 46,500 private sector members.

In about a year, the AHCCCS health plans will be permitted to offer coverage to nonindigents. We have received a

$346,261 grant from the Robert Wood Johnson Foundation to offer prepaid coverage to small employee groups and that program will begin October 1, 1987.

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REFERENCES

1. Orient JM: Correction: The Arizona Health Care Cost Containment System (Correspondence). West J Med 1986 Sep; 145:394
2. Orient JM: The Arizona Health Care Cost Containment System—A prepayment model for a national health service? (Correspondence). West J Med 1986 Jul; 145:114-119

Criticism of the California Alpha Fetoprotein Screening Program

To the Editor: I write in strong support of the opinions expressed by Drs Stillman and Hoffman in their correspondence regarding the California Alpha Fetoprotein Screening Program.[1] In offering the option of this test to my obstetric patients, I share the fact that the likelihood of a neural tube disorder, in the absence of positive family history, is far less than the likelihood of many other fetal anomalies, that children with spina bifida are not retarded and often benefit from rehabilitation and that the test results are less than 100% reliable. The overwhelming majority of my patients decline AFP testing. I note with interest that most patients of those colleagues I have queried on this subject, to the contrary, choose to undergo this test.

The decision whether or not to test for any particular disorder in any patient must be individualized, based primarily on the clinical judgment of the responsible treating physician. Widespread, cost-ineffective, government-mandated programs such as the Swine Flu Vaccination Program and the California Alpha Fetoprotein Program do a disservice to our profession and to our patients. I urge the early termination of the latter program.

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REFERENCE

1. Stillman PC, Hoffman JK: AFP anxiety (Correspondence). West J Med 1986; 145:393

* * *

To the Editor: I am writing to add my voice to those of Drs Stillman and Hoffman who express their criticism of the California Alpha Fetoprotein Screening Program in the September issue.[1]

As an obstetrician who initially welcomed this program, I have suffered the disillusionment of watching several patients endure the trauma and anxiety of finding out that they have a "positive" test. The problem might not be so bad except that they receive the information in the form of a cold, computerized letter from the state. Instead of reporting the findings to the physician, as has been the time-honored tradition of other laboratories, these bureaucrats feel they have a right to communicate directly with patients. This results, in many cases, in near hysteria over being told that something may be wrong with one's baby.

I have already taken the trouble to express my concerns to the administrators of this program but, as I might have expected, they have not responded. Therefore, I have adopted a policy which I would recommend to others who are concerned about this. Henceforth, I no longer include the patient's address with her specimen. Instead, I substitute my office address so all communication must come to me. This way, I feel I can reduce the trauma to the patient and better prepare her for the additional testing required.

I would hope that the administrators of the California AFP Program would realize that the limit of their responsibility is to perform laboratory tests and that the interpretation of these tests and the communication of their results to patients is the responsibility of the private physician.

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REFERENCE

1. Stillman PC, Hoffman JK: AFP anxiety (Correspondence). West J Med 1986 Sep; 145:393

Matters Gaseous

To the Editor: In "Downwind Update—A Discourse on Matters Gaseous" in the October 1986 issue,[1] Dr David F. Altman first states that it is his purpose to bring us up to date in an area in which our understanding has literally exploded in the past several years, and then he goes on to write that "It is probable that air swallowing has very little to do with the amount of gas present in the gastrointestinal tract."

Dr Altman ignores what was learned a great many years ago by a classic experiment: the esophagi of several dogs were ligated, therefore obstructed, so that no air could be swallowed. X-ray films were taken before and after; within a few hours virtually all of the gas in the gastrointestinal tract had disappeared. And, as every radiologist knows, whenever there is a mechanical obstruction at any level in the gastrointestinal tract, there is distention above and there is reduction or elimination of gas, at times complete, below the site of obstruction.

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REFERENCE

1. Altman DF: Downwind update—A discourse on matters gaseous (Medical Staff Conference). West J Med 1986 Oct; 145:502-505

* * *

To the Editor: In his informative and entertaining article[1] in the October 1986 issue, Dr Altman gives clinicians several pearls that are of value in dealing with flatulent patients.

He does not, however, discuss the role of allowing flatus to be passed as it may be medically therapeutic as opposed to the more common practice, in this society, of repressing the urge to pass flatus when with one's peers.

Is there evidence or is it hypothetically reasonable to suspect that repressed flatulence is a significant factor in the diverticular disease or any other of the intestinal maladies of our contemporary society?

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REFERENCE

1. Altman DF: Downwind update—A discourse on matters gaseous (Medical Staff Conference). West J Med 1986 Oct; 145:502-505

Dr Altman Responds

To the Editor: Thank you for the opportunity to respond to the letters concerning my Medical Staff Conference article, "Downwind Update."[1]

The role of air swallowing in the production of flatus or of symptoms of "excess" intestinal gas is at best minor. Studies by Levitt and his colleagues, cited in the October 1986 article, of the composition and volume of intestinal gas support this conclusion, especially the data that show the relatively small amount of nitrogen and large amount of carbon dioxide and hydrogen in intestinal gas. Dr Tolone points out studies supporting this concept. The important idea that the volume and composition of gas at any point are the product of multiple factors, including swallowed air, gas production, absorption and elimination, is the lesson to be derived from the illustration accompanying the article.

Dr Sommer's hypothesis that flatus retention is important in the pathogenesis of diverticular disease was first put forth by Wynne-Jones[2] but has not received general support. I believe most practitioners would be reluctant to advise patients against this practice which is probably common in so-called civilization. Certainly one must balance one's obligations to the individual patient against those to society at large. Such ethical dilemmas are beyond the scope of this author.

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REFERENCES

1. Altman DF: Downwind update—A discourse on matters gaseous (Medical Staff Conference). West J Med 1986 Oct; 145:502-505

2. Wynne-Jones G: Flatus retention is the major factor in diverticular disease. Lancet 1975; 2:211-212

Heparin Added to Infused Fluids

To the Editor: The article "Catheter-Related Septic Central Venous Thrombosis—Current Therapeutic Options," published in the August issue,[1] while interesting, was disappointing. The authors made no mention of the potential for prevention of this complication by a simple technique. Heparin added to infused fluids has been shown to be effective in reducing thrombosis and sepsis in indwelling catheters. In a prospective study, Fabri and colleagues[2] showed that the addition of 3,000 USP units of heparin per liter of total parenteral nutrition solution reduced the incidence of thrombosis from 31.8% to 8.3%. This was achieved without any significant difference of anticoagulation effect.

Furthermore, in a large group of morbidly obese patients undergoing gastric bypass operations (whose veins are difficult to cannulate), I have routinely added 1,000 USP units of heparin per liter of peripheral intravenous solution. This has permitted use of the original vein catheter for a full five days (when the patients start taking fluids by mouth), with a minimal incidence of phlebitis. Not only has this been less burdensome for the patients, it has saved nurses the frustration of restarting intravenous lines. It has *not* led to any complications.

It is my opinion this technique can be used safely for *all* patients requiring three to four days of parenteral feeding, as it would obviate the need to change lines every 48 hours as is routine in many hospitals.

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REFERENCES

1. Kaufman J, Demas C, Stark K, et al: Catheter-related septic central venous thrombosis—Current therapeutic options. West J Med 1986; 145:200-203

2. Fabri PJ, Mirtallo JM, Ruberg RL, et al: Incidence and prevention of thrombosis of the subclavian vein during total parenteral nutrition. Surg Gynecol Obstet 1982; 155:238-240

Elderly Patients With Dementia

To the Editor: Dr Heikoff has done a service by again bringing forth appropriate concern for care of elderly with dementia or dementia-like syndromes.[1] In addition to underlining in her review that about 20% of elderly with dementia will have a partially or fully treatable underlying cause, further observations are in order regarding depressive, "pseudodementia."

When depression is the sole active culprit of the dementia-like syndrome, not only mood but cognitive impairment will be greatly or completely improved with successful treatment with medications or electroconvulsive therapy. Even where a presumptive early dementing syndrome, otherwise irreversible, is present, improvement of the endogenous depression will substantially improve current cognitive function. Although side effects must be viewed in context, even the presence of an actual dementing disorder should not exclude use of medicines or electroconvulsive therapy as otherwise indicated for the mood disorder.

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REFERENCE

1. Heikoff LE: Practical management of demented elderly. West J Med 1986 Sep; 145:397-399

* * *

To the Editor: In her article "Practical Management of Demented Elderly" in the September issue,[1] Lisa Heikoff offers several suggestions that appear to me to be anything but practical. My comments below apply to the 90% of demented elderly with irreversible disease.

First, Dr Heikoff suggests that the demented patients regularly undergo routine (and presumably she means comprehensive) medical screening. Given the limited value of a digital rectal examination, should a demented patient undergo sigmoidoscopy? I think not. Would I really treat breast cancer, ovarian cancer or colon cancer in the hopelessly demented patient? Once again, I doubt it, unless the patient was suffering from symptoms secondary to these diseases, in which case I would attempt to palliate only and keep the patient comfortable.

Second, the author advocates monitoring mental status with formal psychological testing, and referral to a psychiatrist or neurologist for the same. It seems to me that these expensive tests are about as useful as counting candles on a birthday cake—decline is documented for all the world to see but nothing is materially changed.

Third, she recommends consultation with a psychiatrist or psychologist for diagnosis of depression as a contributing factor to dementia. When all is said and done, the

patient either responds favorably to an antidepressant or does not. Involving yet another care giver (a practice Dr Heikoff later decries) is hardly necessary and, once again, expensive.

Dementia is almost inexorably progressive, frustrating to treat and a terrible burden on the patient's family and no doubt on the patient. I have found that a caring family, a supportive nursing staff and the physician's willingness to advise are all that are necessary and useful. I would wonder if other primary care physicians feel the same.

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REFERENCE

1. Heikoff LE: Practical management of demented elderly. West J Med 1986 Sep; 145:397-399

* * *

To the Editor: I have read, with interest, the article, "Features of Potentially Reversible Dementia in Elderly Outpatients" by Larson and co-workers.[1] I found the work done by the authors to be quite helpful in making the point that *all* patients with dementia, no matter their age or living status, deserve a comprehensive workup to look for potentially reversible conditions. My only exception to the authors' approach is that nowhere in the article is the value of computerized tomography (or magnetic resonance imaging) of the brain mentioned.

Computed tomography and magnetic resonance imaging of the brain are noninvasive, highly efficacious procedures in ruling out such reversible conditions as subdural hematoma, normal-pressure hydrocephalus and brain tumor. While a careful neurological history and examination are important, contemporary technology should not be ignored. True, computerized tomography and magnetic resonance imaging are relatively costly; but the long-term care often required for a patient with deteriorating mental status is far more costly, both in money and, more important, in emotional suffering by the patient and his or her family.

I think that *anyone*, young or old, who presents to a physician with organic dementia, deserves a good neurological evaluation; and that evaluation should include a computed tomographic or magnetic resonance scan of the brain.

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REFERENCE

1. Larson EB, Reifler BV, Sumi SM, et al: Features of potentially reversible dementia in elderly outpatients. West J Med 1986 Oct; 145:488-492

Side Effect of Captopril and Enalapril

To the Editor: I wish to focus *WJM* readers' attention on what appears to be a little-recognized side effect of captopril and enalapril—namely, bothersome coughing.

Reports of Cases

Two patients recently were noted with this problem in our general internal medicine practice.

The first patient, a 62-year-old woman, had been started on a regimen of enalapril maleate for the treatment of hypertension. The day following starting the drug (5 mg per day), a dry, ticklish cough developed that persisted and would awaken her in the middle of the night. This was bothersome enough to require narcotic medications prescribed by her local physician. I saw her after almost three months of this coughing problem. She had had no chest discomforts. Her lungs were clear. Pulmonary function studies showed forced vital capacity (FVC) of 2.4 (94%), and volume of gas forcefully expired in one second (FEV_1) of 2 (92%) before bronchodilator. These were unchanged after bronchodilator. The patient's medication was changed to captopril, 12.5 mg twice a day, and her coughing continued. The coughing did not clear until captopril therapy was also discontinued.

The second patient, a 76-year-old woman with hypertension, was started on a regimen of enalapril, 2.5 mg per day. Very shortly thereafter, she began noting a dry mouth and persistent ticklish cough without sputum production. This kept her awake at night. After four months of this, her medication was changed to captopril, 25 mg twice a day, in place of the enalapril. Her symptoms resolved completely and she was able to continue with captopril without difficulty.

Discussion

In the *Physicians' Desk Reference*, cough is mentioned as an uncommon side effect of enalapril. Dry mouth and dyspnea are listed as possible side effects of captopril but cough is not mentioned.

I believe that readers should be aware of coughing as a potential side effect of these medications. The two medications may or may not cross-react with each other in this regard. Awareness of this potential problem may help avoid lengthy diagnostic workups that may otherwise be unnecessary.

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Correction: Diagnostic Immunopathy

To the Editor: It has been brought to my attention that a manuscript mistake resulted in an error in Table 3 in the UCLA Specialty Conference in the July issue.[1] In that table (page 71) the marker studies for chronic leukemia appeared twice (redundant) and there is a mistake in the repeated part (11B4 should be corrected to B4).

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REFERENCE

1. Cancilla PA, Cochran AJ, Naeim F, et al: Diagnostic immunopathology (Specialty Conference). West J Med 1986 Jul; 145:65-73

Topics in Primary Care Medicine

Fecal Occult Blood Screening and Evaluation for a Positive Test

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The American Cancer Society recommends annual fecal occult blood testing for all asymptomatic persons 50 years of age and older. This testing enhances the identification of disease, including an increased percentage of pathologically earlier cancer lesions—that is, Dukes' A and B stages. As yet, however, no data have shown improved colon cancer survival rates in screened persons. In writing this paper, we assume that early detection of colonic neoplasia by occult blood surveillance is worthwhile and that ongoing long-term clinical trials will eventually show the survival benefit of this practice.

Fecal occult blood screening of asymptomatic persons yields 2% to 6% positive tests. If annual screening recommendations were universally implemented, 3 million asymptomatic Americans would have a positive result and should receive further testing. Diagnostic evaluations for this group would cost between 500 million and 2.5 billion dollars. Thus, implementing colorectal cancer screening has a major impact on physician time and medical economics. Each asymptomatic patient with a test positive for fecal occult blood should be further evaluated in a thorough but cost-effective manner. Our discussion will focus on these issues and offer a practical approach to the evaluation of these asymptomatic patients.

Methods of Fecal Occult Blood Testing

Seven commercial fecal occult blood tests based on guaiac-impregnated paper currently are available in the United States. Of these, only Hemoccult II has been objectively compared with other techniques—such as labeling erythrocytes with chromium 51 to detect blood loss—and has achieved widespread popularity. Hematest, a preparation based on orthotoluidine, is not recommended due to poor reliability, as it yields more false-positive and false-negative results. Several new methods for more specific or sensitive occult blood detection have been developed, and their usefulness is being explored. HemoQuant, a quantitative assay based on the conversion of heme to fluorescent porphyrins, is more sensitive for hemoglobin. Another test using immunochemical methods with anti-human hemoglobin also has a high true-positive rate free of cross-reaction with foodstuffs, animal hemoglobins and drugs. Both of these tests are technically complex, costly, time-consuming and not yet applicable for general use.

Effective cancer screening requires patient acceptance. The return of Hemoccult cards is frequently low, ranging from 26% in a mass screening program to 75% in a highly motivated patient group followed in a private practice setting. Developing screening methods in which the aesthetic aspects of stool sampling are improved may also increase compliance. An example of this is the recently released Coloscreen Self-Test, a chemically treated paper pad that is placed in the toilet bowl after a bowel movement and changes color to indicate a positive reaction. The patient is responsible for interpreting the test and reporting a positive result to the physician. There are only limited data suggesting concordance between Coloscreen testing and Hemoccult II, and no studies of Coloscreen Self-Test compliance have been published. Thus, Hemoccult II is currently the best standardized and most practical approach to widespread fecal occult blood screening.

Hemoccult II test paper is impregnated with gum guaiac. When a fecal specimen contains peroxidases or catalases (in-

(Brendler SJ, Tolle SW: Fecal occult blood screening and evaluation for a positive test. West J Med 1987 Jan; 146:103-105)

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Supported in part by US Department of Health and Human Services PHS grant No. D28 PE10057-01.

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cluding hemoglobin), or both, a reaction occurs with hydrogen peroxide in the developer solution. This catalyzes the oxidation of guaiac to a quinone structure, which causes a blue color change. The Hemoccult II slide has a faint color change in the presence of 4 to 6 ml of hemoglobin per 100 grams of feces, which is twice the normal daily fecal blood loss in an adult. Guaiac testing is not specific for human hemoglobin, and a variety of foods and medications commonly affect the results (see Table 1). Other agents may also affect test interpretation under special circumstances. Cimetidine often produces a false-positive test of gastric aspirates but does not affect stool specimens. Povidone-iodine, used as a topical antiseptic or douche, may cause false-positive results due to oxidation by iodine, whereas the use of laxatives may increase the frequency of both false-positive and false-negative results. Of note, barium sulfate in the stool does not influence the reaction, nor does the use of a high-residue diet. Factors known to affect guaiac testing should be avoided starting 48 hours before the first stool collection and not resumed until all the stool specimens have been obtained. For screening purposes, specimens should not be taken if blood is actually seen in the stool, or urine, or if a patient is menstruating.

Using a protocol for stool collection and testing as listed in Table 2, the false-positive rate for Hemoccult II is acceptably low at 1% to 3%. The cost impact of small deviations from this type of protocol is significant. If, for example, an underlying 1% true-positive rate is assumed, with 1% false-positives, about 50% of positive Hemoccult tests will come from patients with neoplasia (cancer or polyps). With 3% false-positives, only 25% of positive Hemoccult tests will come from patients with neoplasia. Moving from a 1% false-positive rate to a 3% false-positive rate will substantially increase the cost of a screening program.

Because fecal occult blood testing relies on active bleeding to detect colonic lesions, a significant number of nonbleeding, minimally or intermittently bleeding lesions will be missed. To minimize the number of bleeding lesions missed, ascorbic acid must be avoided and slides must be returned promptly for immediate testing. A strong reaction will remain positive for at least ten days, whereas specimens with weakly positive reactions may yield negative or equivocal results after two or four days of storage. This is presumably due to desiccation of the fecal specimen with time. Attempts have been made to increase the sensitivity of Hemoccult II to peroxidases by rehydration. Sensitivity improves, but specificity decreases, as rehydration produces more false-positive readings. Thus, it is not a generally recommended procedure.

Even when used optimally, Hemoccult II misses as many as 65% to 75% of colonic polyps and 10% to 30% of cancers. This has led the American Cancer Society to recommend flexible sigmoidoscopy as a complementary screening procedure. When carried out to 60 cm, sigmoidoscopy can detect greater than 60% of colon cancers and 60% of colonic polyps. This procedure can be done safely by community-based pri-

TABLE 1.—*Factors Affecting the Results of Hemoccult II Testing*

Drugs and Dietary Restrictions	*Justification*
Aspirin or nonsteroidal anti-inflammatory drugs	Increased fecal blood loss in healthy persons documented by ^{51}Cr-labeled erythrocyte studies
Ferrous sulfate or ferrous gluconate	Several small studies suggest a higher rate of false-positive tests for healthy persons using ferrous salts
Ascorbic acid	Fecal excretion of ascorbic acid (>55 mg/day) inhibits Hemoccult reaction
Rare red meat (beef, lamb)	Excluding rare red meat (250 grams steak/day) from diet led to a significant fall from 6.1% to 1.6% in Hemoccult positivity
Fresh vegetables, fruits high in peroxidase	Peroxidase in 5 to 10 grams of uncooked radish, horseradish, cantaloupe or cauliflower has an activity equivalent to 1.0 ml of blood

TABLE 2.—*Protocol for Stool Sample Testing*

Two days before the first stool collection and continuing throughout the collection period, avoid ingestion of aspirin, nonsteroidal anti-inflammatory drugs, vitamin C, iron, laxatives, rare red meat and fruits and vegetables high in peroxidases (Table 1).*

Beginning on the third day of the diet, take two specimens from three consecutive stools.

Promptly return the three completed Hemoccult cards (six samples).

Test samples promptly.

Evaluate all positive results.

*Other foods with moderately high peroxidase content (cucumbers, carrots and grapefruit) should be avoided in excessive amounts.

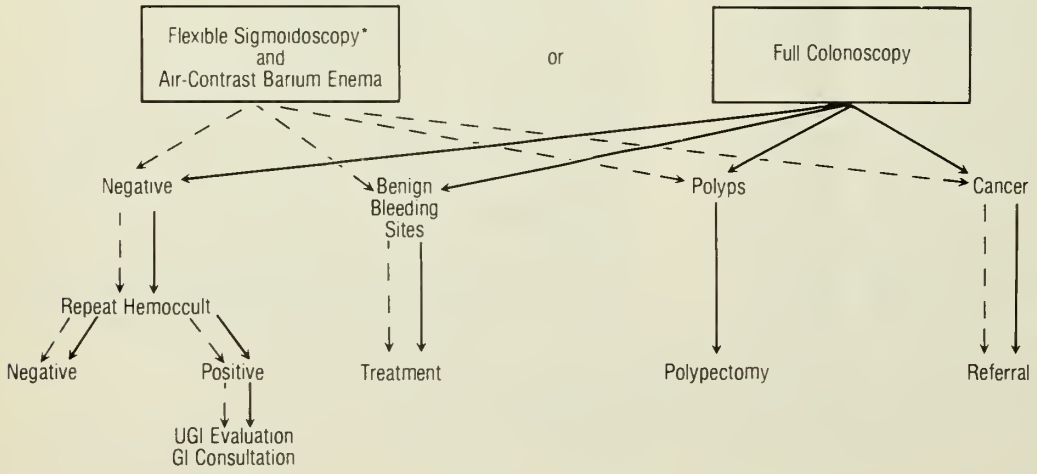

Figure 1.—Evaluating an asymptomatic patient with a Hemoccult-positive test. *If polyps are found by flexible sigmoidoscopy, then an air-contrast barium enema should be replaced by full colonoscopy. GI = gastrointestinal, UGI = upper gastrointestinal [tract]

mary care physicians in asymptomatic Hemoccult-negative patients with a diagnostic yield of 10% neoplasia (9% polyps, 1% cancer).

Evaluation for Tests Positive for Fecal Occult Blood

Once a screening Hemoccult test is positive in an asymptomatic patient, it cannot be ignored, and further evaluation is warranted. Subsequent negative Hemoccult tests do not adequately rule out neoplasia, as bleeding can be intermittent. The challenge lies in choosing the best procedural algorithm that will detect the highest percentage of colonic polyps and cancer with the least risk and the lowest cost. Controlling costs means minimizing the direct costs of the procedure and physician fees and the indirect costs of complications of the procedure, patient anxiety, time lost from work and evaluation for false-positive tests. Physicians must also consider the relative strengths and availability of resources in their communities.

Two approaches meet these needs: (1) flexible sigmoidoscopy to 60 cm, plus air-contrast barium enema, or (2) full colonoscopy (Figure 1). If colonoscopy is done initially, it provides an adequate identification of colonic pathology. It generally is the most sensitive procedure for detecting polyps. If colonic preparation is poor, however, or if the colonoscope is not able to reach the right side of the colon, as many as 10% of polyps may be missed. The major risk of colonoscopy is perforation, which occurs in about 3 per 1,000 patients screened. This rate is about tenfold higher than the perforation rate of a barium enema. But because colonoscopy has the major advantage of using one procedure to endoscopically examine and take a biopsy of the rectosigmoid and more proximal colon, it is being used more frequently for the initial evaluation of patients with a positive Hemoccult test. Because colonoscopy is usually done by gastroenterologists or surgeons, a limitation is accessibility to the procedure. In some communities, flexible sigmoidoscopy and air-contrast barium enema (ACBE) are more practically done than colonoscopy.

Flexible sigmoidoscopy can be done by primary care physicians as well as specialists. It is preferable to rigid sigmoidoscopy because it leads to the detection of at least twice as many polypoid lesions. Patients with flexible sigmoidoscopic examinations in which the results are normal or who have benign bleeding sites identified should then have a good-quality ACBE. Patients with rectosigmoid polyps should bypass the ACBE and have a full colonoscopy to detect and remove any additional polyps. If cancer is found on flexible sigmoidoscopy, the patient should have an ACBE or full colonoscopy to further define the tumor involvement and rule out synchronous colon cancer, which occurs in 4% to 6% of these patients.

The air-contrast barium enema, if done with adequate colonic preparation and radiologic technique, is as sensitive (92% to 98%) as colonoscopy in detecting carcinoma of the colon, excluding anal or rectal lesions and in situ cases. It has the advantage of providing a permanent record of each examination. If the colonic cleansing is poor, however, or if a single-column barium enema is done, as many as 30% of Dukes' C and D tumors and 60% of Dukes' A and B tumors may be missed by barium enema. In addition, ACBE is less sensitive for detecting polyps. Several studies comparing ACBE and colonoscopy have shown that ACBE may miss 25% to 50% of polyps less than 1 cm and 10% to 25% of polyps greater than 1 cm. About 85% of the radiologically undetected polyps larger than 5 mm, however, are located in the sigmoid colon and flexible sigmoidoscopy complements ACBE by detecting polyps in this location.

Assuming strict adherence to the protocol of stool sampling as in Table 2, about half of asymptomatic patients with a positive Hemoccult test will have significant colonic neoplasms, with polyps larger than 5 mm outnumbering cancers (38% versus 12%). Of the total number, 30% will have benign sites of possible colorectal bleeding identified—such as diverticulosis, polyps smaller than 5 mm, internal hemorrhoids—and 20% will have normal lower gastrointestinal tract studies. This latter group of patients should undergo repeat Hemoccult testing followed by upper gastrointestinal tract evaluation or consultation with a gastroenterologist if tests are persistently positive. Hemoccult testing is relatively specific for lower gastrointestinal tract bleeding. About 80% of asymptomatic patients with a positive Hemoccult test will have a colonic bleeding site identified by a thorough evaluation.

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Forum

The Aim of American Medicine Within the Constraints of Today's Society

In the August 1986 issue the editors began a forum for discussion of the aim and purpose of medicine within the constraints now being placed on health care. A summary will appear in a future issue.

What Patients Expect

CARTER G. MOSHER, MD

MUCH HAS BEEN WRITTEN in recent years about the declining prestige of American medicine. Paradoxically, this public disenchantment has mounted during a period of unprecedented advancement in medical science. One critic (Aaron Wildavsky) has been prompted to draw an analogy with the patient who is "doing better, but feeling worse." Understandably, physicians are asking themselves, "Just what do they expect from us anyway?"

Respect cannot be gained merely by insisting that it is due. We are well advised, I believe, to look within ourselves to reaffirm those qualities that have traditionally earned high social esteem for members of the medical profession. The lesson is inescapable that patient satisfaction relates more directly to the personal touch of a physician than to the impact of modern technology. In my view, society will continue to value those physicians:

1. Who can place their patients' interests ahead of their own convenience;
2. Who offer more than knowledge and skill, namely the energy and dedication to apply them in day-by-day contact;
3. Who take the time to communicate their advice as well as their compassion;
4. Who consider how they can heal, where possible, and how they can help in any case.

The practice of medicine is truly an extension of one's intellect and attitude; an extension, let me suggest, in the active sense of reaching out to make one's services available. Ideally, the physician is a composite of the informed professional and a caring human being. To the extent that we can remain sensitive to the personal concerns of our patients, we will be giving them not only the best that modern medicine has to offer, but also the confidence that they have a doctor to whom their state of health really matters. Those physicians who heed this calling will surely bring honor to themselves and to their profession.

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(Mosher CG: What patients expect, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:106)

A Nuremberg Defense

GLENN S. VANSTRUM, MD

DURING THE PAST DECADE vast changes have occurred in the economic, political and technologic practice of medicine. Nevertheless, in spite of DRGs, PACs and MRIs, we still care for the sick. In the shadow of Hippocrates, we still strive to uphold a moral tradition. In the hospital trenches, we still battle death and debility.

(No real change there.)

Gradually big business and big government are telling us more and more what we must do, or what we must desist from doing. As we slowly lose financial control, we physicians might still be optimistic that the public respect and admiration the medical profession has built through generations of dedicated travail will somehow keep us well cared for on a material basis.

(We hope, at least.)

Really, all we need to do is follow the directive of government and assist getting the health industry's newly inflated 10% of the GNP back to a more reasonable 6% or so.

(Cost-cutting *is* a buzzword these days.)

We should surely just get back to work caring for the sick, do our jobs, and let our wise political and economic leaders take charge.

(Well, let's not let them push us around *too* much. After all, what about the quality of care?)

Perhaps we might want to ask, for what exactly is the rest of that GNP being used? Does it build Hondas, Sonys, Nikons, BMWs and Mercedes?

(No, probably not.)

Does it build cruise missiles, MIRVed Minutemen, "Peacekeeper" MXs, B-1 bombers and neutron bombs?

(Oh, no. You're one of those antinuclear nuts!)

What is the purpose of having a clever nuclear deterrent of 5,728 submarine nuclear warheads, 1,027 ICBMs with 2,127 warheads and some 3,500 strategic bomber nuclear devices?

(To keep the Russians from bombing us, of course.)

We are spending billions to upgrade our weapons so they can target the Russians' 6,012 nuclear weapons in 1,398 missiles. Is there a reason to do this, if, say, we were already attacked by the Russians and those silos of theirs were empty?

(No—but what does this have to do with medicine?)

Then the United States is, essentially, condoning a first-strike nuclear weapon philosophy.

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(Vanstrum GS: A Nuremberg defense, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:106-107)

(Whatever it takes to show those evil, God-less Commies.)

Most experts agree the US has some 30,000 nuclear devices, strategic and tactical, the USSR some 20,000, and France, Britain, China and Israel some more. If a Challenger-Chernobyl type of technology failure occurred, there is a real chance someone might get hurt. And, with most of these weapons cocked and poised at each other on 30 minute warning. . . .

(Well, ha-ha, we'd win then. Our four touchdowns and a safety over their three TDs and a missed extra point, 30-20.)

Given the communications problems submarines have, and such a phenomenon as the electromagnetic pulse (well documented radiation effect of atmospheric nuclear explosion which causes sustained electronic havoc), it is very probable a "small" nuclear exchange would escalate into an all-out exchange.

(We learn from experience, then.)

Carl Sagan and other physicists predict that a "mere" 100 megaton exchange would precipitate the global year-long climactic change called a nuclear winter.

(But do we really know that?)

Most medical authorities predict global destruction of life following such an exchange, and possible extinction of our own species.

(Oh, these long-hair beatnicks and hippies have been carrying those "The End Is Near" signs for years.)

While the Strategic Defense Initiative (Star Wars) is pleasing intellectually, it seems unlikely a determined opponent would not be able to sneak a few hundred megatons or so through.

(So?)

When one couples the SDI defense system with our MIRVed (multiple independent reentry vehicle) silo busters and submarines with which it is doubtful command will be able to communicate after hostilities begin—why, we see that we have a system built primarily for *first strike*. Isn't there something a bit immoral about planning this?

(It's not our business as physicians to worry about this!)

If our country and the USSR are pursuing a first strike strategy that is expensive and genocidal, do we not, as physicians, have a moral duty to band together and get our global patients onto a healthier regimen?

(I just do as I am told. Let the experts in the political/military/industrial world handle it. I'm going back to the hospital.)

You've been very patient. One last question, please. Suppose, as a physician, you survived a nuclear bomb explosion. What would you do about the hundreds of thousands of burn, trauma, starvation, radiation and disease victims?

(You're just trying to scare me. You've obviously been influenced by the Communists. Go back to work. Do as you are told.)

Medicine's Problems Reflect Society's

EDWARD PALMER, MD

THERE IS AMPLE historical support for the view that the problems plaguing today's American medicine followed sequentially federal legislation designed to improve and extend its benefits to the citizenry. The recognition of its wayward consequences is indispensable to the rethinking of medical care fundamentals. Such rethinking should include not only how to adapt to the present reality of the practice of medicine but also how to limit, neutralize or prudently counteract its disruptive and hampering effects on health care and enhance the public's insight as it grows in understanding of what can be expected from government.

Your previous contributors agree on the fundamentals of professional conduct. We should also agree upon a pluralism of ethical medical approaches to satisfy desired choices, needs and means—both of the patients and ourselves. Pluralism is dominant in our society. It is what gives individualism its quality and is basic to social tranquility.

The enactment of Medicare disregarded the realism of our varied financial means. It was the philosophic turning point in the provision of medical care to a segment of our population. Our long-term aim should be Medicare's dismantling with the expansion of Medicaid (the AMA's original Eldercare proposal somewhat altered) to take care of the financially needy seniors. The political flak could be somewhat neutralized by noting that 52% of Medicaid patients are Medicare beneficiaries. It will be slow and difficult but worthwhile.

The search for means to adapt to the restraints of present-day medicine aside, our problems cannot be separated from the other pervasive changes affecting our society as a result of our flawed economic and political policies. As a learned profession, our greatest concern should be with the looming placebo-treated economic upheaval—the continuing spending beyond our imagination or understanding, the monumental debt and our monetary policy solutions. An economic shambles threatens our form of government! Common sense suggests we make our own preparation for a medical Grace Commission when the most severe and crippling belt tightening becomes inevitable. Unless my understanding is totally flawed, that's where we should examine the gaping cracks in our entire social framework.

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(Palmer E: Medicine's problems reflect society's, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:107)

Educate, Educate, Educate

R. W. ODELL, Jr, MD

WHETHER WE PHYSICIANS agree or disagree, our society has decreed through its collective bureaucracies that a kind of ceiling has been reached for the funding of our health care enterprise. This event is forcing a long needed reappraisal of values we as physicians have taken for granted. How important is it to sustain mere physical existence? Are biotechnological solutions adequate, or even appropriate, in the healing of most illnesses? Can we, as organized medicine, justify these expenditures when so many other needs in our society cry out for funding? Medicine has not been honest about these issues with the larger culture. We have "taken the money and run," as Woody Allen would say. As long as third parties were around to pick up the tab, we were free to go our merry

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(Odell RW Jr: Educate, educate, educate, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:107-108)

way, treating the physical manifestations of illness without having to ask too many embarrassing questions about efficacy or cost-effectiveness.

In some sense, the organizations of American medicine bear the same relationship to the body politic that the individual physician bears to his patient. A competent physician educates his patient as part of his treatment. American medicine will regain its preeminence in our society only insofar as it reassumes this vital function of educator about matters medical. This will require a brutal honesty and much soul-searching, for past deficiencies are not easily made up.

Initially, we must tell our constituency that biomedical intervention has been oversold as a solution to the healing of illness. We have not wrought miracles, we have merely performed some amazing technical feats that are only of limited usefulness to a fortunate few. The use of technical solutions as the sole means of treating illness and disease will never "cure" us; not only is this approach doomed to failure, but its wide application carries the substantial risk of generating ". . . a new kind of suffering: anesthetized, impotent, and solitary survival in a world turned into a hospital ward" (Ivan Illich, *Medical Nemesis*, Pantheon, 1976).

Second, biomedical intervention comes with a price tag, and therefore no one has an absolute "right" to its potential benefits. As a commodity much like automobiles, shoes, deodorant or toilet paper, its price and availability are subject to the law of supply and demand. Only by subsidizing the cost of biomedical intervention through third party payment schemes has the medical care consumer been shielded from the direct economic impact of escalating prices secondary to increased utilization.

Third, we must reemphasize how important the role of individual judgment is in deciding on appropriate treatment. Because payment schemes emphasize procedures unduly, experience and judgment have not been accorded their proper place in the medical decision-making process. When to do a procedure, what procedure to do, and how well a procedure is done are of more importance in determining quality care than whether or not a procedure is done.

Fourth, we must reeducate ourselves as to the true nature of the healing transaction. Are we merely biotechnicians, manipulating serum concentrations of chemicals or removing diseased tissue and organ systems? Or can we again become physicians in the sense Jacob Needleman speaks of in his book, *The Way of the Physician*—"a man who has both magnetism and conceptual knowledge . . . inner being and outer knowledge in stable harmony," offering our patients what only we can give, the healing power of "concentrated attention"?

The physician perspective can be exceedingly valuable to society, for we speak not only as medical experts, but also as sometime patients and knowledgeable citizen taxpayers. Our collective voice will only be heard and heeded, however, when we speak honestly, truthfully and clearly. Self-promotion and media blitzes may seem attractive in the short run, but ultimately they only serve to obfuscate. Instead, the aim of American medicine within the constraints of today's society should be to educate, educate, educate.

Aggressive Concern for Society as a Whole

MURRAY KLUTCH

As one who devoted a greater part of his working life working for, and on behalf of, physicians but can now view their problems and concerns somewhat more objectively after several years of retirement, I find your series of articles illuminating and yet short of the mark. Illuminating in that some of the contributors have correctly focused on the need to identify with the humanistic values and concerns of the patients American medicine has once again begun to emphasize, rather than on the technological and scientific aspects with which medicine has been identified in the past. The fears of competition, government domination and control, the threat of other disciplines, the loss of individual esteem and initiative, and criticism over physicians' charges and incomes reflect some of the concerns of those who engage in the day-to-day practice of medicine.

But if medicine is to become the "pilot" that Dr White proposes in his Forum article in the October issue, it must assume more than an identification with the psychosocial interests of patients. *It must publicly demonstrate its abiding and aggressive concern with the health, safety and welfare of society as whole—state, United States and world.*

The greatest threat to humanity is the threat of war; a nuclear war whose dark shadows hover over the lives of all people, including those of physicians who deal with their daily problems and those of their patients.

American medicine can assume the greatest undertaking of its history by becoming a vital and active force for peace, for disarmament, for cessation of nuclear weapons, for joining forces with physicians throughout the world in voicing their opposition to war. By so doing it will have earned the respect and gratitude of the American public as a leading exponent of a nuclear-free world. This is the kind of leadership American medicine must take despite other constraints of today's society if it is to achieve the heights of respect and acclaim it once reached—and can still attain.

There is evidence of such a growing movement in many countries throughout the world. *The Western Journal of Medicine,* which has previously devoted special issues of wide interest to its readers, would be performing a greatly needed service by informing physicians of the greatest threat to their survival, their profession and that of mankind by dedicating such an issue to the importance of peace in our lifetime and that of the future.

Such unique and bold leadership would, indeed, not go unrecognized.

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(Klutch M: Aggressive concern for society as a whole, *In* The aim of American medicine within the constraints of today's society—A forum. West J Med 1987 Jan; 146:108)

Seminars in Health Care Delivery

A Practitioner's Guide to Treatment Selection in Psychiatry

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This feature will appear regularly in The Western Journal of Medicine. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

Psychiatry has changed dramatically during the past 20 years, probably as much as any other medical specialty. What had been largely a clinical art is now becoming very much a clinical science. A research rigor and creativity have informed all aspects of psychiatric investigation and practice. The basic neuroscience research carried out within psychiatry has become perhaps the most exciting of any basic science research in medicine.[1] A new and innovative classification system was introduced in 1980 and has for the first time provided for highly reliable psychiatric diagnoses.[2] Each of the psychiatric disorders is now defined by a list of operational diagnostic criteria, providing clear-cut algorithms to guide the process of differential diagnosis. Clinical outcome trials in psychiatry have become highly sophisticated in solving many of the technical design problems in patient selection, treatment delivery, process and outcome measurement and in providing meaningful controls.[3] A large number of psychiatric treatments have been developed and found to be effective.

As might be expected, the image of psychiatry has lagged far behind its actual pace of development. Many physicians were trained at a time when psychiatry was able to offer little more than a special insight into the physician-patient relationship and support for those who suffered with emotional illness. Moreover, for all kinds of reasons, psychiatry has also been a convenient topic for jokes and a target for disparagement. Such estrangement is certain to be resolved in the near future as psychiatrists establish their special areas of investigative, diagnostic and treatment expertise and as all physicians become aware of the advances that have occurred in the field and of their wider implications for medical practice.

This article provides a practical guide for psychiatric treatment selection for general medical practitioners. We discuss the evidence for the efficacy of various psychiatric treatments, suggest the kinds of patients who might benefit from psychiatric treatment, what psychiatric treatments are available, who should deliver them and how one differentially selects from among the available possibilities in developing a treatment plan for a particular patient. Space constraints require that this be a brief overview; interested readers are referred to much fuller discussions of these topics that we have presented elsewhere.[4-6]

The Efficacy of Psychiatric Treatments

The psychiatric literature now contains literally thousands of controlled-outcome studies. These can be grouped into several different categories. There is a vast literature documenting the effects of various kinds of medication for the various types of psychiatric disorder. The same Food and Drug Administration criteria that govern the development and testing of all other medications have been applied in testing the medications most commonly used in psychiatry—that is, the neuroleptic, antidepressant and anxiolytic drugs and lithium. The evidence from the many carefully controlled, double-blind studies is unequivocal. These medicines are definitely effective and relatively safe when used for appropriately selected patients. A rough average over thousands of trials with different drugs for different psychiatric conditions would probably result in a response rate of some 60% to 70% in those patients who receive medicine, whereas the placebo response tends to range from 20% to 40% (and lower for patients with schizophrenia).[7] Moreover, there are several different families of neuroleptic, antidepressant and anxiolytic drugs, and if patients fail to respond to a trial with any given drug, or experience intolerable side effects, they may still go on to have a good response with a different type of neuroleptic, antidepressant or anxio-

(Frances A, Clarkin J, Perry S: A practitioner's guide to treatment selection in psychiatry. West J Med 1987 Jan; 146:109-113)

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lytic drug. Thus, the overall and eventual response rate may be even higher in clinical practice than it is in research studies, presuming that the medications are prescribed in suitable doses for appropriate patients. The effectiveness of electroconvulsive therapy (ECT) as compared with antidepressants and with placebo—that is, sham ECT—has also been established in numerous studies. Perhaps most important is the fact that many depressed patients who have not responded to antidepressant medication will nonetheless go on to respond well to ECT.[8]

The second category of outcome study has been focused on determining the effectiveness of various forms of psychotherapy. Until recently this issue had been clouded by a polemic, and not particularly useful, controversy. Opponents of psychotherapy claimed it was ineffective with little or no evidence to support this contention, while proponents were enthusiastic about the benefits of psychotherapy with an equally scanty empiric foundation for their beliefs. During the past 20 years, more than a thousand controlled psychotherapy outcome studies were done, but until recently this literature was difficult to interpret because there was no convenient and unbiased method to review and collect data across studies.

This problem has now been solved with the development of a research review method known as meta-analysis. This method is based on using a simple but powerful statistic known as the effect size (computed by subtracting the change on any outcome measure in the control group from the change in the active treatment group and dividing by the standard deviation of change in the control group). It provides a change metric in standard deviation units that can be used to aggregate raw scores across studies. In a review of 475 controlled psychotherapy outcome studies, Smith and co-workers calculated effect sizes for some 1,700 different outcome measures.[7] Their meta-analysis showed that psychotherapy was significantly and substantially more effective than control alternatives (which consisted generally of being put on waiting lists or of nonspecific treatment contacts). In fact, patients at the 50th percentile in the treated groups had made sufficient gains so as to become as well off as patients in the 80th percentile of the untreated groups. Although it is elegant, the meta-analytic method is necessarily limited by the quality of the available studies, which were often done in a fashion that is not up to the current standards of design specificity.[9] Nonetheless, it seems clear from the findings that psychotherapy is an effective treatment.

There is an additional documentation of the efficacy of psychotherapy that will undoubtedly be of great interest to physicians. There is now fairly compelling evidence that psychotherapy produces definite benefits in the treatment of the medically ill, such as reducing morbidity and complications of a medical illness, increasing compliance with a needed treatment regimen and reducing the length of hospital stays and the number of required outpatient visits.[10,11]

The third category of outcome research in psychiatry compares the efficacy of psychotherapy versus medication versus combinations of psychotherapy and medications for the various psychiatric disorders in which both treatments might be used. This question has not yet been sufficiently studied and, in fact, is currently under investigation. Nonetheless, the available data are very interesting. Smith and colleagues applied their meta-analytic method to drug and psychotherapy comparisons and discovered that the effects of combined treatments are greater than the effects of either treatment given alone, and, in fact, the effects of drugs and psychotherapy appear to be additive when these are given together.[7] The combination of medication and psychotherapy appears to be particularly effective in affective and schizophrenic disorders.[12-14]

Who Should Be in Psychiatric Treatment?

There are several lines of evidence that suggest very clearly that many persons who would benefit from psychiatric diagnosis and treatment do not receive it. This is of special interest here because such persons do see nonpsychiatric physicians who are thus in a position to make crucial diagnoses of psychiatric conditions and to provide referral or treatment.

The most compelling data are from a recently conducted National Institute of Mental Health epidemiologic catchment area study carried out collaboratively in several different cities.[14] The study applied rigorous methods for identifying a randomly selected epidemiologic sample of the general community to make diagnostic decisions. Perhaps the most interesting finding of this massive study was that, across cities, there was a fairly high lifetime prevalence of anxiety (15%), affective disorders (8%) and substance abuse disorders (17%). Moreover, most of these persons with clear-cut and often very treatable psychiatric disorders had never received treatment for them.[15] Our own experience confirms this finding. Whenever there is a television program or a prominent newspaper article on anxiety or affective disorder, our clinic is likely to receive 100 or more phone calls from persons who have for the first time recognized that they have one of these disorders. They are more likely previously to have brought their complaints to nonpsychiatric physicians. It is thus crucial that nonpsychiatric physicians learn how to diagnose these conditions and either provide treatment themselves or arrange for referral.

Another line of supporting evidence that nonpsychiatric physicians see many patients who could benefit from psychiatric treatment is the consistent finding from many studies that as many as 50% of persons who present in general medical practice complain of symptoms that are primarily emotional in origin.[16] They often receive anxiolytic or antidepressant medication from their nonpsychiatric physicians, but very frequently this is provided with unclear indications and in doses that are inadequate. Many nonpsychiatric physicians need further training and experience on the indications for and ways of prescribing such drugs.

What Psychiatric Treatments Are Available?

There are many different kinds of psychiatric treatments. These may be delivered in a range of settings (inpatient, outpatient, day hospital); for varying durations (such as consultations on one extreme, a lifetime follow-up on the other); in differing formats (individual, group, family), and with varied orientations (somatic, psychodynamic, cognitive, behavioral or interpersonal). To complicate matters even further, there are many viable permutations of all of these different possibilities. We can provide here only the briefest

overview of this diversity and will deal only with the various orientations.

The somatic orientation addresses the fact that many psychiatric disorders have a strong biologic component as evidenced by genetic loading, abnormal neuroendocrine and physiologic findings, abnormal responses to biologic challenge tests, positive responses to somatic treatment and, in a few instances, structural abnormalities revealed with sophisticated brain imaging tests. Effective somatic treatments (such as drugs) have been developed for schizophrenia and other psychotic disorders, unipolar and bipolar affective disorders, anxiety and eating disorders, some types of violence and some personality disorders.[17] Somatic treatments should always be delivered along with medical supportive psychotherapy to enhance compliance and the positive expectations that underlie the placebo effect.

The psychodynamic psychotherapies focus on clarifying the unconscious psychological conflicts that are responsible for some psychiatric symptoms and for many personality traits. A patient becomes more aware of the ways in which previously warded off and unacceptable wishes and fears are responsible for behaviors and symptoms. Such treatments can often be brief and focused (for instance, 12 sessions over 3 months), but if the goals are ambitious, they may require a greater frequency of visits (more than once a week) and a longer duration (a year or more). Psychodynamic treatments are particularly helpful in promoting character change.[18]

Cognitive therapies focus on the irrational, automatic thoughts that underlie many psychiatric disorders, such as the pessimism and self-criticism of depressive patients or the expectation of patients with anxiety disorders that something bad is always about to happen. A patient learns to identify these irrational thoughts as they occur, subject them to more rational inquiry and reverse the effects they previously had on feelings and behavior.[19] An offshoot of the cognitive approach has been the development of psychoeducational interventions that teach patients about their diagnosis, the physiology and psychology of their symptoms, the various treatment options and prognosis. Often psychiatric patients become secondarily demoralized about their symptoms, blame themselves for causing the problems and begin to feel hopeless. Learning that a disorder is well known, common and treatable is often a great relief and an important first step toward full participation in treatment and recovery.

Behavioral approaches operate on the assumption that symptoms result from the maladaptive reinforcement of self-defeating behaviors that can be unlearned by the teaching of new behaviors. Perhaps the most characteristic behavioral technique is systematic exposure to anxiety-producing situations. This often results in reducing both anxiety and phobic avoidance and in the development of much higher tolerance for whatever anxiety remains.[20] Behavior therapy for depression focuses on increasing a patient's pleasurable experiences. Other forms of behavior therapy include assertiveness training, role modeling and contingency contracting. Behavioral and cognitive techniques are increasingly being combined within one treatment package. These methods usually require from 10 to 40 sessions.

Interpersonal psychotherapies focus on the power of the therapeutic relationship to support a patient through stressful times and also to help the patient to change pathologic styles of interaction. Interpersonal difficulties that occur outside of treatment can be explored and related to interpersonal patterns that develop within the treatment. A therapist attempts to behave toward the patient in a way that will model and pull for new and more adaptive styles of interaction.[21] Interpersonal methods can be delivered within the individual format but are also particularly suited to marital and group psychotherapies.[22]

Most psychotherapists provide some combination of the different models we have just described, but are particularly expert in just one or two of them. In making referrals, it is useful to know something about a therapist's training, experiences and orientation to match these with a patient's particular problems and goals. We will discuss referral options in more detail in the next section.

Who Should Provide Psychiatric Treatment for Patients?

The question of who should provide psychiatric treatment for patients is a highly controversial one with important quality-of-care and financial implications. In current practice, patients in need of psychiatric care are treated by psychiatrists, nonpsychiatric physicians, psychologists, social workers, nurses, activities therapists, marriage counselors, pastoral counselors and, in some states, by persons with no special training or discipline at all who yet claim to be psychotherapists. This situation is confusing to both practitioner and patient. We will attempt to articulate an approach to this question that makes sense to us but which may not work or apply in all situations or make sense to those who have a background different from ours.

Nonpsychiatric physicians who look for them will almost certainly find many patients who suffer from depression, anxiety, somatization disorder, substance abuse and other psychiatric disorders that are severe enough to warrant a treatment intervention. Those nonpsychiatric physicians who have a special interest, and who have received training, in the management of one or more of these conditions may be quite effective in providing the first line of treatment themselves (usually medication and a medically oriented supportive psychotherapy). A consultation with a psychiatrist may be useful at the onset of treatment and is certainly indicated for all of those patients who do not respond to treatment or in whom side effects or complications develop. Even the majority of nonpsychiatric physicians who will refer most or all such patients elsewhere for treatment must have enough training and experience to make the diagnosis that a psychiatric problem is present and that a referral is indicated for further diagnosis and treatment.

For patients who will require medication, the choice of practitioner is fairly straightforward—it will generally be either a psychiatrist or nonpsychiatric physician. For patients receiving psychotherapy, the choice may seem bewildering and spans all of the professions (and even nonprofessions) mentioned earlier. It is often wise to have a psychiatric consultation at the beginning of treatment to determine that medication is not indicated. Beyond this there are few clear guidelines in choosing the discipline of a psychotherapist. The individual personality characteristics, special training and experience of the people involved may be more crucial than the particularities of discipline. It is generally wise to

refer to persons who have received formal training in psychotherapy and who are certified in their discipline. It is also a good practice to check with colleagues to identify therapists with good track records. Patients who have previously been referred can be a good source of information about the styles and results of the therapists they have seen. Fringe therapists and therapies are best avoided.

Differential Therapeutics in Psychiatry

The topic of differential therapeutics in psychiatry is complicated by the fact that a number of different treatments in psychiatry have shown efficacy for the various major syndromes and there is not yet extensive literature indicating which treatment or treatment combinations work particularly well in which situations. One encouraging implication of this is that if one treatment does not work, there is likely to be another available that will. The following is necessarily a telegraphic and impressionistic overview.

The treatment of schizophrenic disorders usually requires a long-term (perhaps lifelong) follow-up. Treatment with medication is necessary for all acute episodes. There is some debate whether medication should be withheld or reduced between episodes in selected patients to reduce the risk of tardive dyskinesia. This is now a subject of intense study. Further, there is good evidence that behavioral family therapy, designed to teach problem-solving skills and to reduce hostile interactions, has a substantial impact in reducing relapse rates.[23] Various forms of rehabilitation therapy also appear promising.

Lithium is the most valuable medication in reducing the cyclicity of bipolar disorder and for the treatment of acute mania. Antidepressants are often necessary to give in conjunction with lithium in treating the depressive phase of bipolar disorder, and it is occasionally necessary to administer neuroleptic agents or electroconvulsive therapy. in the short-term management of a manic phase. Manic patients generally cannot be treated outside of the hospital unless their symptoms are mild and there are unusually strong family supports. Psychotherapy of various sorts may be helpful between episodes to identify and help deal with the psychosocial stressors and the personality factors that may predispose to acute episodes. Psychotherapy may also be helpful for the acute depressions associated with bipolar disorder, if these are not severe.

Antidepressant drugs are more useful for the management of severe melancholic depressions and often hospital admission is necessary. Patients with delusional depression respond best to combinations of antidepressants and neuroleptics or to ECT. Various types of outpatient psychotherapy (particularly cognitive and interpersonal) appear to be very helpful for mild to moderate depression. Patients who have vegetative symptoms of depression or who do not respond sufficiently to psychotherapy may show additional benefit with a combination of antidepressants and psychotherapy.

Patients with panic disorder with and without agoraphobia respond to antidepressant medications, to behavioral therapies and to a combination of these. The choice among these types of treatment depends most on patient and physician preferences. Medications require prolonged use and may result in withdrawal relapses, but behavior therapy requires more in the way of patient motivation and a willingness to enter into feared situations. Anxiolytic drugs are effective for generalized anxiety disorder but carry an appreciable risk of tolerance and abuse in this population. Behavioral, cognitive and psychodynamic therapies appear to be beneficial for generalized anxiety, but this has not yet been established. Obsessive-compulsive and eating disorders respond to both antidepressant medications and behavior therapy, and it is not yet clear when to choose one approach or the other, or a combination.

The milder personality disorders are most often treated with psychodynamic approaches, although cognitive, behavioral and interpersonal approaches also show promise. There are very tentative suggestions that medications may sometimes be helpful for patients with schizotypal and borderline personality disorder.

Issues having to do with the choice of the setting, duration and format of psychiatric treatment are beyond our scope here and have been discussed elsewhere in considerable detail.

Conclusions

Psychiatric disorders—particularly anxiety, affective, substance abuse and personality disorders—are commonly encountered in general medical practice. Advances in psychiatric classification have taken the mystery and unreliability out of psychiatric diagnosis. Because simple and effective treatments exist for many of these disorders, it is incumbent on medical practitioners to become familiar with the psychiatric diagnostic criteria of those psychiatric cases that are most often encountered in their practices. It can be just as serious a medical mistake to miss a diagnosis of depression (with its 10% lifetime suicidal rate) or panic disorder (with its frequent complication of agoraphobia) as it is to miss congestive heart failure or an enlarged spleen. Those physicians who prescribe psychiatric drugs (neuroleptics, antidepressants, anxiolytics, lithium) should—and often do not—have sufficient training on their indications, dosage regimen and side effects to use them intelligently. Without such training, psychiatric referral at least for consultation increases the chance that a patient will receive up-to-date treatment. Psychotherapy has documented its efficacy and is useful in treating patients with a variety of psychiatric diagnoses, stress response syndromes, personality problems and miscellaneous problems in coping.

Psychiatry has recently developed a strong foundation in clinical and basic science and has drawn closer in its methods and attitudes to the other specialties of medicine. This has already benefited psychiatry greatly and will undoubtedly also benefit the rest of medicine as soon as recent advances in psychiatry become part of common medical knowledge.

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The Distribution of Services to the Underserved

A Comparison of Minority and Majority Medical Graduates in California

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We assessed the belief that minority physicians are more likely to serve traditionally underserved minority populations by examining the medical practice profiles of minority and majority physicians who graduated from seven California medical schools in 1974 and 1975. The results indicate that minority graduates are more likely to locate their practices in areas with health care personnel shortages (53%) than are majority graduates (26%). Minority physicians had a higher proportion of Medicaid or Medi-Cal patients, and they saw a greater percentage of minority patients (60%) than did majority physicians (21%). We conclude that minority graduates of US medical schools, at least those from California, serve traditionally underserved populations to a greater degree than do their majority graduate colleagues. These findings lend strong support to the contention that aggressive affirmative action programs by medical school admission committees serve the important utility function of improving the distribution of medical services.

(Davidson RC, Montoya R: The distribution of services to the underserved—A comparison of minority and majority medical graduates in California. West J Med 1987 Jan; 146:114-117)

In the past 20 years, minority enrollment in US medical schools has increased significantly. In 1968 only 3.6% of all US medical students were minorities.[1(p13)] The largest percentage of these were black students (2.7%, or 75% of all minority students), and three quarters of the black students were concentrated in two institutions with traditional and specific commitments to the education of black physicians, Howard University College of Medicine (Washington, DC) and Meharry Medical College (Nashville).[1(p1)] By the 1983-1984 academic year, minority student enrollment in US medical schools reached 15%, with a 16.8% representation in the entering class.[2,3(pp1-3)] In the same year, enrollment of underrepresented minorities—blacks, Chicano/Mexican-Americans, American Indians, mainland Puerto Ricans—as defined by the Association of American Medical Colleges (AAMC), rose to 11.1%.[3(pp1-3)]

Although many factors have contributed to this increased enrollment of minority medical students, a large part of the increase has been the result of deliberate policy decisions and a concerted national effort to recruit and train minority students. The Federal Health Career Opportunity Program has infused millions of dollars into US medical schools for minority recruitment and retention. Discussions leading to the formation of medical school policies on recruitment and admission of minority students have typically centered on issues of equity or parity.[4-6] Equal educational access for minorities became a major objective, born of a collective sense of fairness. Policies resulting from this concern serve an "equity function," and evaluation of their success has been available through examination of the proportions of medical school applicants, enrollees and graduates who are minorities and comparing these with the general population.

A second focus for policy discussions has concerned the belief that minority physicians may be more likely to serve minority populations. Statistics continue to show a disparity in life expectancy between whites and minorities, and minority populations are more likely to be living in areas with health care personnel shortages.[7(p1)] It has been argued that an increase in minority physicians will have the effect of bringing needed services to traditionally underserved areas. Thus, an increase in the percent of minority graduates of US medical schools would have a positive medical value, serving a "utility function" beyond the issue of fairness. In a recent article, Keith and co-workers assessed the effects of affirmative action programs by studying the 1975 graduating class from all US medical schools.[8] They found a greater percentage of minority graduates practicing in federally designated areas of health care personnel shortages and a greater

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percentage of minority patients in the practice population of minority physicians when compared with their majority colleagues. This study adds to the one of Keith and associates by a more in-depth look at the practice characteristics of California medical school graduates.

The long lead time associated with medical education has delayed the effects of the recently increased minority student enrollment on physician practice and patient care patterns. Consequently, the assumption that increased minority enrollment leads to increased medical services to traditionally underserved populations has remained difficult to assess. Those studies that have measured the ethnic profile of patients cared for by minority physicians have not had the opportunity to compare minority physicians with a majority control group. The purposes of our study was to measure differences in practice characteristics of minority and majority graduates of California medical schools to evaluate the utility function of increasing the number of minority medical school graduates.

Methods

Three hypotheses were developed as the basis of this study:

1. Underrepresented minority graduates from California medical schools are more likely to practice in or adjacent to areas in California with health care personnel shortages than are majority graduates.
2. Underrepresented minority graduates from California medical schools are likely to serve a higher percentage of patients supported by Medi-Cal (Medicaid) or other public assistance payment programs
3. Underrepresented minority graduates from California medical schools are likely to serve a higher percentage of minority patients than are majority graduates.

The physicians selected for this study are graduates from seven of California's eight medical schools. Graduates of the eighth school are not included because the religious mission of the school leads its graduates to undertake overseas missionary assignments and because relatively few minority students graduated from this school during the study years. Of the remaining seven schools, five are publicly funded and two are private institutions.

The minority graduate study group consisted of all students included in the AAMC definition of underrepresented minorities—blacks, Chicano/Mexican-Americans, American Indians, mainland Puerto Ricans—who graduated from one of the seven California schools in either 1974 or 1975. These two years were chosen because they are among the earliest years in which a significant number of minority students graduated from California's medical schools, and because enough time has elapsed for the graduates to have completed residency training and established a practice.

Each school was asked to provide us with a list of all graduates from 1974 and 1975 and to identify each graduate who was a minority according to the AAMC definition. One school declined to release this information without first receiving written permission from its minority graduates. Results of the questionnaires from these minority persons who had given written permission were later analyzed to determine if there were any differences in responses when compared with the other minority graduates.

After the minority study population was identified, the comparison majority study population was selected. Using a statistical random sampling method, an equal number of majority graduates was chosen from the total number of 1974 and 1975 majority graduates from all seven California medical schools. The final study population included 144 minority graduates and 145 majority graduates.

A mail survey instrument was developed and pretested on minority and majority graduates from years not included in the study population. After pretesting, the questionnaire was mailed to both groups in the study. To avoid response bias, the survey instrument made no reference to the purpose of the study other than that it addressed important public policy issues concerning medical education. A follow-up questionnaire was mailed two weeks later to nonrespondents. After an additional two weeks had elapsed, a fourth-year medical student telephoned those persons who had not yet responded to solicit their participation in the study.

California Health Manpower Shortage Area criteria were used to compare the practice locations of graduates. The California Health Manpower Policy Commission was established by the California Legislature in 1973 and is charged with the responsibility of designating areas in California as having a shortage of health care personnel. The commission has divided the state into 249 medical service study areas using census county divisions as the unit of analysis. In rural areas, these census county divisions are aggregated in a rational manner so that no area is more than 20 constructive miles from a community population center. In urban areas, the census county divisions are subdivided along census tract lines, recognizing neighborhoods with similar demographic characteristics. These urban subdivisions generally include a population of between 20,000 and 150,000.[9]

Once these medical service study areas have been identified, a shortage of health care personnel is declared if the physician-to-population ratio is greater than 1:1,967. Other criteria, such as percent of the population 65 years and older, percent of the population below the US Census Poverty Index and extreme distance to the nearest medical service location are also considered when designating a medical service study area as underserved.

Because of this somewhat artificial division of communities, particularly in urban areas, medical service study areas that are not designated as underserved but are immediately adjacent to those areas that are underserved were included in this study definition as locations that serve underserved populations. Those medical service study areas that are not adjacent to an underserved area and are not designated by the commission as medically underserved were defined as locations that do not serve underserved populations.

Results

A total of 289 questionnaires were mailed to potential respondents and 138 were returned, for a 48% response rate. Of 144 minority graduates, 66 returned questionnaires, for a 46% response rate; of 145 majority graduates, 72 replied, for a 50% response rate. The difference in the ratio of respondents to nonrespondents for minority and majority graduates was not significant (χ^2, $P > .05$, no significance).

The response rates for schools were similar, with the exception of the one school that required permission from each minority graduate to be included in the study. In all, 19 mi-

nority graduates from this school agreed to participate and 18 returned their questionnaires. According to AAMC records, 46 minority students graduated from this school during the 1974 and 1975 study years. Therefore, the minority graduate response rate for the school requiring individual permission was 39%. This was lower than the 46% response rate for minorities from all other schools. The response rate for the majority graduates from the school requiring minority consent agreements was 49%, which is consistent with the rate for the total majority study group. This was expected, as the method for selecting majority graduates of this school was no different from that at the other schools. Questionnaire responses for minority respondents from this school were compared with all the other minority respondents. For the questions pertaining to location of the practice in or adjacent to a medically underserved area, and to percent of practice reimbursed by Medi-Cal (Medicaid), there was no statistical difference (χ^2, $P > .01$, no significance) between the two groups. Minority graduates from the school requiring consent agreements, however, did report having practices that included higher percentages of patients from various ethnic backgrounds than did the minority graduates of the other six schools (χ^2, $P < .01$). Since these respondents knew that the study concerned minority graduates and their practices, their responses may have been biased.

Practice Location

Minority graduates practicing in California were more likely to be located in medical service study areas, or in immediately adjacent areas, that are designated as having health care personnel shortages. Although questionnaires were mailed to graduates who practiced both in California and in other states, only the practice addresses of the California-based physicians were analyzed. Of the 45 minority graduate respondents practicing in California, 24 (53%) met the underserved/adjacent criterion compared with 14 of the 53 (26%) of the majority graduate respondents (χ^2, $P < .01$). There was no significant difference between minority and majority graduates in the likelihood of their remaining in California.

Medicaid Practice

Minority graduates had a higher percentage of public assistance patients in their practices than did the majority graduates. All graduates were asked what percentage of their total practice consisted of Medi-Cal or Medicaid patients, and their responses were given in 10 percentile point categories. A total of 64 minority graduates and 70 majority graduates answered this question. The 64 minority graduates answering this question described their Medicaid patient population as follows: 21 (33%) saw less than 10% Medicaid patients, 12 (19%) had between 10% and 20%, 11 (17%) had between 20% and 40%, 12 (19%) had between 40% and 70% and 8 (13%) had between 70% and 99+% Medicaid patients. The 70 majority graduate respondents described their Medicaid patient populations as follows: 41 (59%) saw less than 10%, 12 (17%) had between 10% and 20%, 10 (14%) had between 20% and 40%, 4 (6%) had between 40% and 70% and 3 (4%) had between 70% and 99+% Medicaid patients. Figure 1 illustrates these results. A pooled contingency table indicated a significant difference between the two groups of graduates (χ^2, $P < .02$).

Ethnicity of Practice

Minority graduates saw a higher percentage of minority patients than did majority graduates. Minority graduates reported the average ethnic composition of their patients as follows: 39.6% majority patients (including Asian patients), 23.5% black, 33.1% Hispanic and 3.7% "other." Majority graduates reported an average patient mix of 79.5% majority patients, 6.7% black, 12.5% Hispanic and 1.3% "other" (Figure 2). The χ^2 test was applied and statistical significance was confirmed ($P < .01$).

The profile of patients was also analyzed comparing the ethnicity of the provider with the reported practice patient mix. Black graduates reported seeing 33.3% majority patients, 50.6% black patients, 14.5% Hispanic patients and 1.3% "other" patients (Figure 3). Hispanic graduates reported having a patient mix of 42.4% majority patients, 7.7% black patients, 46.8% Hispanic patients and 2.8% "other" patients (Figure 4).

Comments

The results of this study support the proposition that underrepresented minority medical graduates serve traditionally underserved populations to a greater degree than do their majority graduate colleagues. Minority graduates maintain practices that serve a significantly higher percentage of

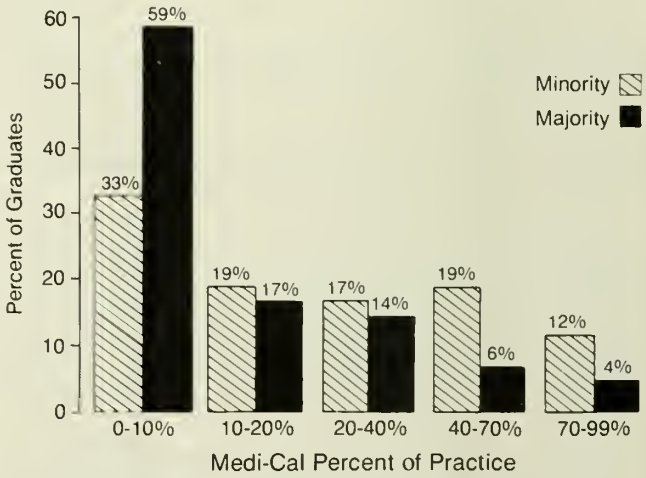

Figure 1.—Comparison of percent of Medicaid (Medi-Cal) patients in minority and majority practices in California.

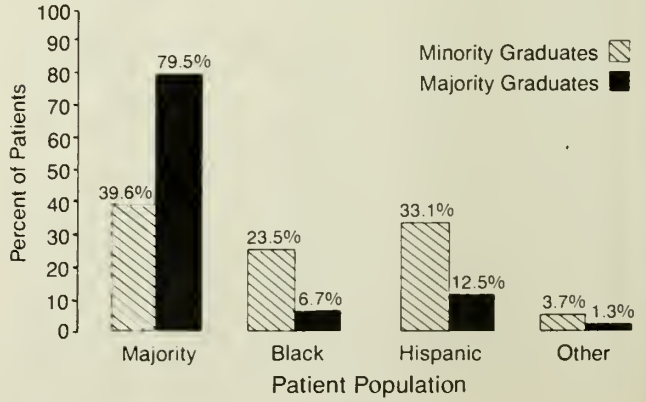

Figure 2.—Comparison of ethnic composition of minority and majority graduate practices.

blacks, Chicano/Mexican-Americans, Medicaid recipients and patients from underserved geographic locations. These findings are, of course, highly interrelated. Areas of California that have the highest percentage of Medi-Cal patients also have large minority populations and are more likely to be declared medically underserved.[10,11]

There continues to be significant discussion regarding influences on physician practice locations.[12] The issue of physician practice location in areas where there are high percentages of ethnic minorities has been studied extensively over the years.[13-15] Lieberson found that physicians of a given ethnic group locate their offices in accordance with the residential distribution of their ethnic group.[15] Guzick and Jahiel found that nonwhite or non-American physicians tend to locate their offices in areas having a population that is ethnically similar to their own.[13] It has been shown by others that black physicians serve a larger percentage of black patients than do majority physicians.[5,6,16,17] It is not surprising that our study found a similar relationship between Hispanic physician graduates and the populations they serve. Language capability may be a major contributor to Hispanic patients' preference for Hispanic physicians.

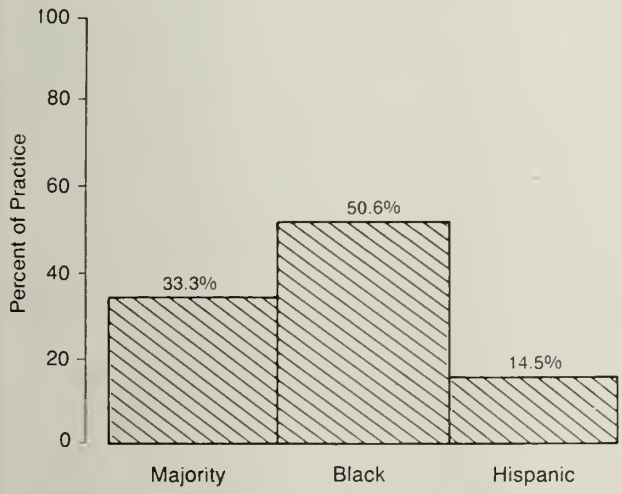

Figure 3.—Ethnic profile of patients of black graduates.

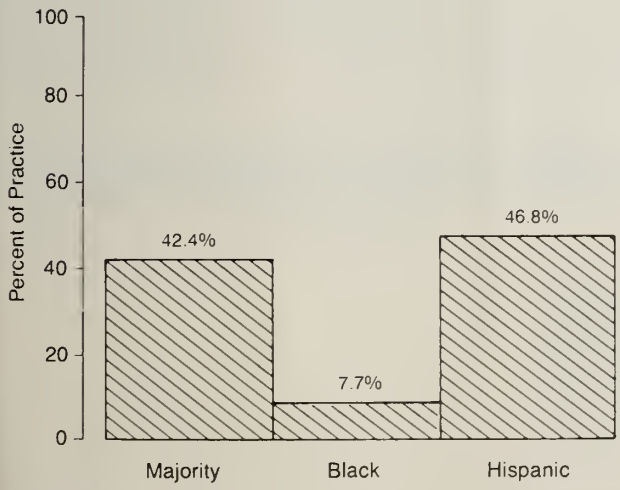

Figure 4.—Ethnic profile of patients of Hispanic graduates.

A disproportionately high percentage of minority residents is located in areas designated in California as medically underserved.[11] Elesh and Schollaert suggest that physicians' desire to practice in locations with their own ethnic identity group can overcome the competing negative income and status factors associated with areas with a high percentage of minorities up to a yet-undefined real income loss, at which point income becomes the predominant factor. Our findings that minority medical school graduates have more minority patients and are more likely to locate their practices in, or adjacent to, underserved areas are consistent with this conclusion.

Findings from this study and others such as the study by Keith and associates[8] lend strong support to the contention that aggressive affirmative action programs by medical school admission committees serve an important medical function—increasing the number of physicians most likely to deliver services to the traditionally underserved. To those admission committee members in US medical schools who each year ask the question "why?" in reference to strong affirmative action programs, this study adds more evidence that the answer lies in a combination of fairness (equity) and greater service to underserved populations (utility).

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Commentary

Nora's 'Living Will'

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

Nora had lived 84 years, enjoying a full and fruitful life. She loved children, her own and everyone else's, playing their games with them throughout her fourscore years. Her son called her the "oldest teenager on the block." And now we three attending physicians were sitting across a conference table from Nora's son, trying to answer the questions he threw at us: "What good is my mother's 'living will' if you doctors won't honor it? Why can't you abide by Mother's wishes and let her die?"

His sturdy 84-year-old Scandinavian mother, Nora, had been in robust health until the evening she came into the emergency room, laid low by a perforated gastric ulcer. Now almost a month had passed, and Nora was hanging onto life by a slim thread, owing to what seemed to be insurmountable postoperative complications. She had been semicomatose for 3¼ weeks and was now supported by a ventilator, oxygen, intravenous administration of fluids and an ensemble of exotic antibiotics.

A member of the family had located a living will that Nora had signed nine years ago, and now we two surgeons and an internist were being asked to abide by the wishes she had expressed almost a decade ago. But we were hesitating, remembering that such a will had to be renewed every five years. We had to assume, therefore, that our hands were tied because the will was outdated. We also recalled that a living will was defined as a directive made by a patient who was suffering from a "terminal" condition such as cancer. But our patient was dying of cardiorenal failure due to peritonitis and therefore did not fall into the proper "terminal" category.

Because of these two considerations—the out-dated will and the lack of evidence of a terminal condition at the time the will was signed—we were on the horns of a legal dilemma. It seemed easiest to procrastinate.

Finally, under family pressure, we cautiously withdrew part of the artificial life support—the ventilator, the tube feeding, the antibiotic medications—but we just could not bring ourselves to go all the way and turn off the oxygen—to "pull the plug."

And so Nora, gasping, struggling for every breath, clung to that thin thread of life.

At last a sister, the eldest member of the family, no longer able to watch this suffering, drew on her stalwart Swedish courage and demanded that *all* artificial life support be removed. After an hour-long conference with our ethics committee and another with the entire family, we gave in to their wishes and discontinued giving the oxygen; 3½ hours later, Nora stopped struggling for breath and quietly slipped from this earthly life.

In retrospect, we physicians realize that because of our timidity we had caused needless anguish by not being willing to give up sooner. And what a waste of time and money. We could plead for forgiveness on two counts: First, because by training and tradition, we are compelled to preserve life at all costs; and, second, because the litigious climate we live in saps us of our courage.

Ironically, on the day after Nora's death, our state legislature decided to amend the Natural Death Act. Now the Act provides that (1) no longer is there the requirement that a person preparing a living will must be suffering from a terminal condition, and (2) the five-year limitation is eliminated. This directive now takes the form of what is legally defined as a "durable power of attorney."

The Noras of the future may now be spared the anguish of prolonged dying. As surrogates, the family members may assert their decision-making rights. And we physicians may act with forthright courage—and kindness.

(Fox ERW: Nora's 'living will.' West J Med 1987 Jan; 146:118)

Dr Fox is in private practice in Coeur d'Alene, Idaho, and is the Special Editor for Idaho.
Reprint requests to E. R. W. Fox, MD, 1401 E Lakeshore Dr, Coeur D'Alene, ID 83814.

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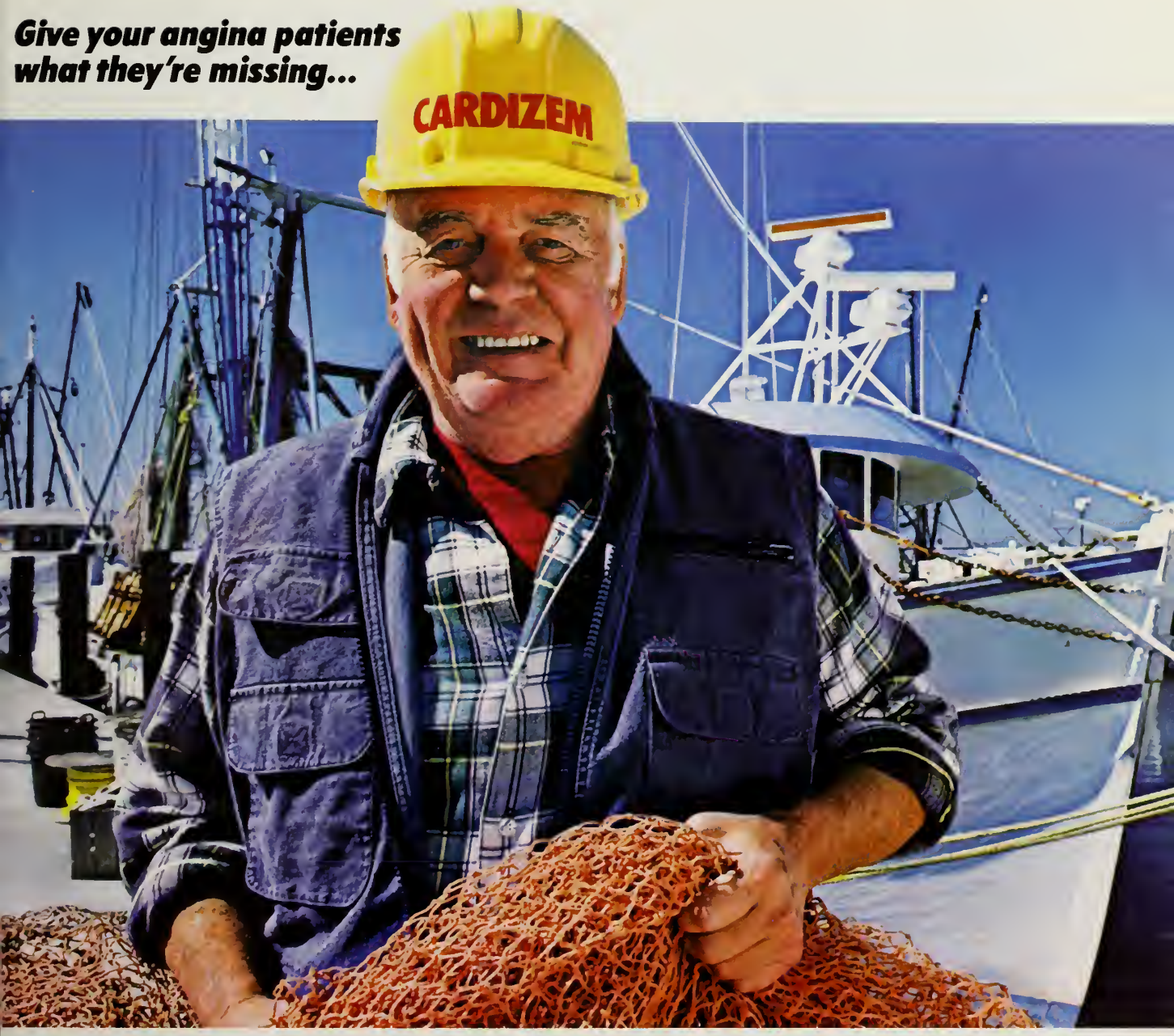

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2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System:	Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria
Other:	Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 7/86

See complete Professional Use Information before prescribing.

References: 1. Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347 **2.** Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159 **3.** Johnston DL, Lesoway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985,55:680-687 **4.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39 **5.** Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982,50(Sept):94-116

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(Continued from Page 36)

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 2-4—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Monday-Wednesday. Fee: $400. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 2-4—**Neuroradiology Update.** UCSD at Hotel Del Coronado, Coronado. Monday-Wednesday. Fee: $350. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 2-6—**The Annual Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation at Hyatt Lake Tahoe, Incline Village, Nevada. Monday-Friday. 20 hrs. Fee: $385. Contact: John P. McGahan, MD, SRREF, PO Box 19184, Sacramento 95819.

March 3-5—**MRI for Technologists.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Thursday. 15.5 hrs. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 3-6—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Tuesday-Friday. 25 hrs. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 7-8—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. Contact: UCSF.

March 9-13—**30th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. Contact: UCSF.

March 14-15—**Contemporary Trends in Diagnostic Nuclear Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Saturday-Sunday. Contact: UCSF.

March 16-20—**Diagnostic Imaging—1987.** UCSF at Waiohai Hotel, Kauai, Hawaii. Monday-Friday. Contact: UCSF.

April 9-11—**Thoracic Imaging—1987.** UCSF at Hyatt Regency, Monterey. Thursday-Saturday. Contact: UCSF.

April 10-12—**OB/GYN and Abdominal Sonography: Update 1987.** UCSF at Hyatt Regency on Union Square, San Francisco. Friday-Sunday. Contact: UCSF.

April 13-17—**Vascular Imaging.** University of Washington at Royal Lahaina Resort, Maui, Hawaii. Monday-Friday. Contact: Univ of Washington, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 19-25—**7th Annual San Diego Residents' Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sunday-Saturday. Contact: UCSD.

May 1-3—**12 Annual Spring Diagnostic Ultrasound.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 19.5 hrs. Fee: $325. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

May 5-9—**7th Annual Diagnostic Ultrasound Post Conference Seminar.** Los Angeles Radiological Society at Sheraton Princeville Hotel, Kauai, Hawaii. Tuesday-Saturday. 19 hrs. Fee: $395. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wednesday-Saturday. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 14-16—**1987 Radiology US Open Golf Meeting.** UCSF at Hyatt Regency, San Francisco. Sunday-Tuesday. Contact: UCSF.

SPORTS MEDICINE

January 18-23—**Sports Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sunday-Friday. 28 hrs. Fee: $425. Contact: UCD.

January 21—**American Orthopaedic Society for Sports Medicine Meeting.** Moscone Center, San Francisco. Wednesday. 7.5 hrs. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

February 13-14—**Medical and Orthopedic Problems in Sports Medicine.** UCI at Irvine Hilton Hotel. Friday-Saturday. 11 hrs. Fee: $95. Contact: J. Massimino, MD, 896 Town and Country Office Park, Orange 92668. (818) 989-3432.

March 16-20—**Annual University of Hawaii: Sports Medicine.** Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Monday-Friday. 18 hrs. Fee: $300. Contact: Ms Joy Lewis, Box CEW-CCECS, 2530 Dole St, Honolulu, HI 96822. (808) 948-8244.

SURGERY

January 19-21—**American Society for Surgery of the Hand's 1st Winter Meeting.** Pacific Medical Center, San Francisco. Monday-Wednesday. 11.25 hrs. Fee: $270-300. Contact: American Society for Surgery of the Hand, 3025 S Parker Rd, Ste 65, Aurora, CO 80014.

January 19-23—**10th Annual Postgraduate Assembly in Surgery.** UCSD at US Grant Hotel, San Diego. Monday-Friday. 26.5 hrs. Fee: $275. Contact: UCSD.

January 22-24—**9th Annual Surgical Postgraduate Course.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Saturday. 14 hrs. Contact: UCD.

January 23-24—**9th Annual Surgical Postgraduate Course: What's New in General Surgery.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday. 14 hrs. Fee: $175. Contact: UCD.

January 25-31—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

January 30-31—**Update on Uses of Lasers in Urology.** UCI at Long Beach. Friday-Saturday. Contact: UCI.

February 13-14—**Cutaneous Laser Surgery.** Good Samaritan Hospital at Sheraton Harbor Island, San Diego. Friday-Saturday. Contact: Paul D. Indman, MD, 15195 National Ave, Ste 201, Los Gatos 95030. (408) 358-2788.

February 17-19—**Maxillofacial Trauma.** USC. Tuesday-Thursday. 16 hrs. Fee: $500. Contact: USC.

February 22-28—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 5-8—**37th Annual Surgical Forum.** Society of Graduate Surgeons of Los Angeles County at Ambassador Hotel, Los Angeles. Thursday-Sunday. 25 hrs. Contact: Soc of Grad Surgeons, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

March 6-8—**Cruciate Ligament Surgery: Principles and Practice.** Scripps Clinic and Research Foundation at Marriott Hotel, La Jolla. Friday-Sunday. 23 hrs. Contact: Bonny A. Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 8-14—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 18-20—**Preoperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wednesday-Friday. 16 hrs. Fee: $325. Contact: UCSF.

March 30-April 10—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Monday-Friday. 100 hrs. Fee: $1,750. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

April 11-18—**Surgery.** University of Washington at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: University of Washington School of Medicine, Div of CME, Sc-50, Seattle, WA 98195. (206) 543-1050.

April 30-May 2—**American Back Society Spring Symposium.** Anaheim Hilton Hotel. Thursday-Saturday. Contact: Aubrey A. Swartz, American Back Soc, 2647 E. 14th St, Ste 401, Oakland 94601. (415) 536-9929.

April 30-May 2—**Postgraduate Course in General Surgery.** UCSF at San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

May 11-15—**The San Francisco Orthopaedic Review Course.** UCSF at San Francisco. Monday-Friday. 40 hrs. Contact: UCSF.

May 13—**Otolaryngology: ENT Infections.** LLU at LLU. Wednesday. 4 hrs. Fee: $60. Contact: LLU.

May 14-16—**Symposium on the Temporomandibular Joint.** UCSF at Hyatt Regency, Monterey. Thursday-Saturday. Contact: UCSF.

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For additional information, contact:
Linda Fernandez, R.N.
Symposium Coordinator
Heart Institute of Tucson
1200 North El Dorado Place
Ferrari Building Suite 620
Tucson, Arizona 85715-4634
(602) 886-2362

CONTINUING MEDICAL EDUCATION

June 4-5—**16th Annual Neurosurgical Postgraduate Course.** UCSF at San Francisco. Thursday-Saturday. 15 hrs. Contact: UCSF.

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Friday-Saturday. 11 hrs. Contact: UCLA.

June 14-20—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sunday-Saturday. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD. House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

January 16-17—**Cardiology for the Non-Cardiologist.** UCI at Long Beach. Friday-Saturday. 12.5 hrs. Contact: UCI.

January 16-18—**Gynecology Update for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 15 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 18-20—**Physical Examination of the Child Sexual Molest Victim: The State of the Art.** Children's Hospital, San Diego at Hanalei Hotel, San Diego. Sunday-Tuesday. 15.5 hrs. Fee: $200. Contact: Ann Albrecht, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-1700.

January 18-23—**Nevada Academy of Family Physicians Winter Assembly: Living Healthier Longer.** Caesar's Tahoe Hotel and Casino, Nevada. Sunday-Friday. 34 hrs. Fee: $400. Contact: Dottie Batchelor, NAFP, PO Box 7471, Reno, NV 89510-7471. (702) 826-5100.

January 19-21—**Pediatrics for the Primary Care Physician.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 16 hrs. Fee: $275. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (619) 453-6222.

January 20-24—**Intensive Course in Geriatric Medicine.** UCLA at Santa Monica. Tuesday-Saturday. 33 hrs. Contact: UCLA.

January 20-24—**Intensive Course in Geriatric Medicine.** American College of Physicians at Santa Monica. Tuesday-Saturday. Contact: Registration Services, ACP, 4200 Pine St, Philadelphia, PA 19104. (800) 523-1546 or (215) 243-1200.

January 23-25—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego. Friday-Sunday. 20 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

January 26-28—**Recent Advances in Geriatric Medicine: Nutrition and Drug Therapy.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Wednesday. 18 hrs. Fee: $395. Contact: UCSD.

January 28-29—**Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wednesday-Thursday. 21 hrs. Fee: $375. Contact: UCSD.

January 30-February 1—**Primary Care Update—1987: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. Fee: $200. Contact: Bonny Mower, Dept of Academic Affairs, PO Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

January 31-February 7—**Infectious Disease in General Medical and Pediatric Practice.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. One week. 24 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

February 2-7—**UCI Family Practice Refresher Course.** Newport Beach. Monday-Saturday. Contact: UCI.

February 4-7—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Stanford Court Hotel, San Francisco. Wednesday-Saturday. 17 hrs. Contact: UCSF.

February 6-7—**Sexual Science: Bridging the Disciplines with the Master Clinicians.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 12 hrs. Fee: $275. Contact: UCLA.

February 7-14—**Office Pediatrics for Primary Care Physicians.** University of Colorado at Kona Surf Hotel, Kona, Hawaii. One week. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

February 8-11—**1987 Research Study Club Midwinter Conference.** Sheraton Grande Hotel, Los Angeles. Sunday-Wednesday. Fee: $235-275. Contact: Research Study Club, PO Box J, South Pasadena 91030.

February 9-14—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Monday-Saturday. Contact: UCI.

February 13-15—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

February 16-18—**7th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Chemical Dependency/Mental Illness—Issues in Diagnosis and Treatment.** Eisenhower Medical Center, Rancho Mirage. Monday-Wednesday. 17 hrs. Contact: Jacqueline Lycett, Annenberg Center, 39000 Bob Hope Dr, Rancho Mirage 92270-3298. In California, (800) 621-7322, nationally, (800) 321-3690.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. Fee: $450. Contact: STAN.

March 4-6—**37th Annual Course for Physicians in Family Practice: Therapeutic Advances in Family Practice.** Mt Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin B. Jackson, Medical Staff and Education Office, Mt Zion Hospital, PO Box 7921, San Francisco 94120. (415) 885-7261.

March 6-12—**55th Annual Postgraduate Convention.** LLU Alumni Association at LLU. Friday-Thursday. 35 hrs. Contact: Carolyn Wieder, LLU, (714) 824-4633.

March 7-8 and 21-22—**Annual Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Saturday-Sunday. 28 hrs. Fee: $300. Contact: Jan Brooks, 615-27th St, San Franicsco 94131. (415) 826-0533.

March 8—**Pharmacotherapeutic Interventions in the Treatment of Chemical Dependence—Drug Solutions for Drug Problems.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Anaheim. Sunday. 5 hrs. Contact: Sandy Swift, Cal Soc for the Treatment of Alcoholism and Other Drug Dependencies, 3803 Broadway, #2, Oakland 94611. (415) 428-9091.

March 9-13—**Hawaii '87: Critical Issues in Primary Care.** Hawaii Medical Association at Waiohai Hotel, Poipu Beach. Monday-Friday. 20 hrs. Contact: Valerie Murray, Pacfic Institute of Continuing Medical Education, PO Box 1059, Koloa, Kauai, HI 96756. 1 (808) 742-7471.

March 11—**Geriatrics.** Enloe Hospital, Chico. Wednesday. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

March 13-15—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Friday-Sunday. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-20—**Epidemics, Pandemics, and Mass Hysteria: From Antiquity to AIDS.** Kauai Foundation for Continuing Education at Poipu Beach, Kauai, Hawaii. Monday-Friday. 19 hrs. Contact: David J. Elpern, MD, Kauai Foundation for Continuing Education, PO Box 3650, Lihue, HI 96766. (808) 245-1507.

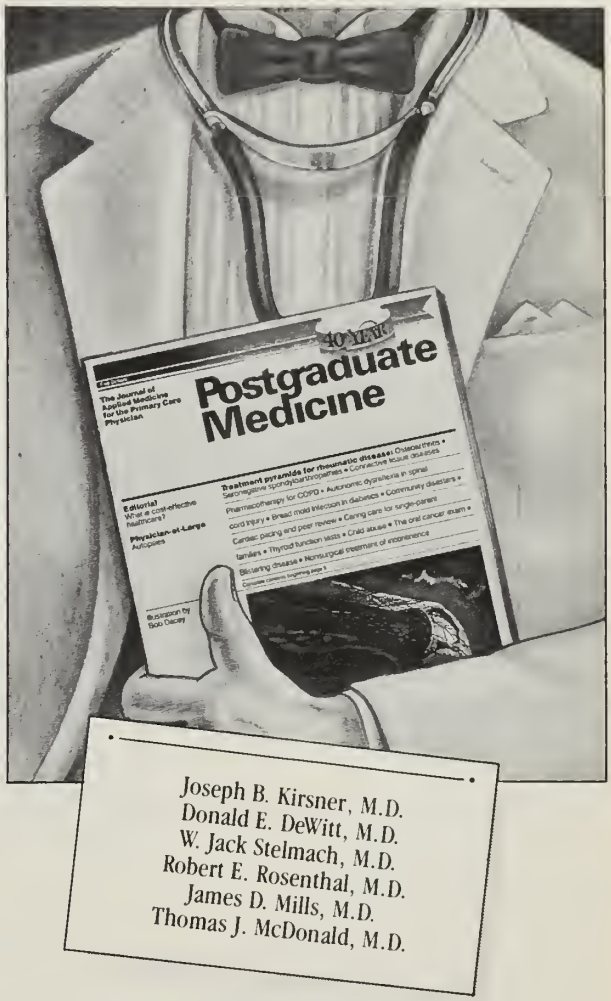
March 19-27—**Specialty Series in Primary Care: Cardiology, Infectious Diseases and Endocrinology.** UCSD at Palm Springs Spa Hotel. Thursday-Friday. Contact: UCSD.

March 26-28—**CPR Update/ACLS Recertification.** UCSF at Holiday Inn Union Square, San Francisco. Thursday-Saturday. 21.5 hrs. Fee: $350. Contact: UCSF.

March 28—**Management of the Menopause: Osteoporosis and Estrogen Replacement Therapy.** Scripps Clinic and Research Foundation at La Jolla. Saturday. 7 hrs. Fee: $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

April 6-10—**Drug Therapy.** University of Washington at Kona Surf Resort, Hawaii. Monday-Friday. Contact: Univ of Washington, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

FAMOUS PHYSICIANS ARE SHOWING UP FOR OUR 40th YEAR CELEBRATION.



Read Every Issue From Cover to Cover:

January
Symposium: Biliary Tract Disease
Special Article: Gastroenterology 1947-1987 ..... Joseph B. Kirsner, M.D.

February 1
Symposium: Focus on Family Practice ..... Donald E. DeWitt, M.D. coordinator
Special Article: Family Practice 1947-1987 ..... W. Jack Stelmach, M.D.

February 15
Symposium: Emergency Medicine ..... Robert E. Rosenthal, M.D. coordinator
Special Article: Emergency Medicine 1947-1987 ..... James D. Mills, M.D.

March
Symposium: Otolaryngology in Primary Care ..... Thomas J. McDonald, M.D. coordinator
Special Article: Otolaryngology 1947-1987 ..... Thomas J. McDonald, M.D.

40 YEAR
Postgraduate Medicine

Every Issue is a Celebration of Clinical Information

April 20-23—**Selected Topics in Dermatology and Pulmonary Intensive Care.** LLU at LLU. Monday-Thursday. 16 hrs. Fee: $400. Contact: LLU.

April 25-26—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, La Jolla. Saturday-Sunday. 13.5 hrs. Fee: $275-400. Contact: UCSD.

May 11-13—**Arthritis Update '87.** Sharp Memorial Hospital, San Diego and UCSD at Hyatt Islandia Hotel, San Diego. Monday-Wednesday. Contact: Mary Belich, Sharp Memorial Hospital, 7901 Frost St, San Diego 92123-2788. (619) 541-3400.

June 8-13—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Monday-Saturday. Contact: UCI.

IDAHO

February 21-28—**Perinatal Medicine.** Sun Valley. One week. Sponsor: University of Washington School of Medicine. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 27-March 1—**Personal Fitness for You and Your Patient: Speakers From the Cleveland Clinic.** Shore Lodge, McCall. Friday-Sunday. Sponsor: Ada County Medical Society. 11 hrs. Fee: $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 24-25—**Annual Family Practice Seminar.** Albuquerque. Saturday-Sunday. Marriott Hotel. Contact: New Mexico Chapter, American Academy of Family Physicians, PO Box 23070, Albuquerque 87192. (505) 298-5300.

February 5-7—**New Mexico-West Texas Urological Society—Annual Meeting.** Albuquerque. Thursday-Saturday. St Joseph Hospital. Contact: Edward L. Johnson, MD, 7000 Cutler NE, Albuquerque 87110. (505) 883-6230.

February 6-7—**Clinical Perspectives in Autoimmune Disease.** Albuquerque. Friday-Saturday. Sheraton Old Town. Contact: Arthritis Foundation, 7520 Montgomery NE, Ste E7, Albuquerque 87109. (505) 883-2964.

February 19-21—**Sports Medicine.** Tammaron. Thursday-Saturday. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

February 20-22—**15th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

February 27-28—**Advances in Internal Medicine VII.** Albuquerque. Friday-Saturday. VAMC Conference Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 5-7—**20th Annual Ob/Gyn Postgraduate Seminar.** Albuquerque. Thursday-Saturday. Hilton. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 11-14—**New Mexico Metabolism Symposium.** Taos. Wednesday-Saturday. Quail Ridge Lodge. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Saturday. Contact: NM Pediatric Society, (505) 758-8651.

March 14—**Perfecting Your Cardiac Physical Diagnosis Techniques: Lessons From a Master—A Symposium by W. Proctor Harvey, MD.** Albuquerque. Saturday. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 19-20—**Cultural Issues in Family Therapy.** Albuquerque. Thursday-Friday. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

April 9-11—**9th Annual Pediatric Cardiopulmonary Update.** Albuquerque. Thursday-Saturday. AMFAC Hotel. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

April 24-25—**Practical Orthopaedics in the Primary Care Setting.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

May 6-8—**New Mexico Medical Society—Annual Meeting.** Albuquerque. Wednesday-Friday. Clarion Four Seasons. Contact: NMMS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

May 15-16—**Biological and Ethical Dimensions of Human Transplantation.** Albuquerque. Friday-Saturday. Contact: Office of Medical Education, Presbyterian Hospital, PO Box 26666, Albuquerque 87125. (505) 841-1225.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave, Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 W Harvard Ave, Roseburg 97470. (503) 673-6641.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued on Page 127)

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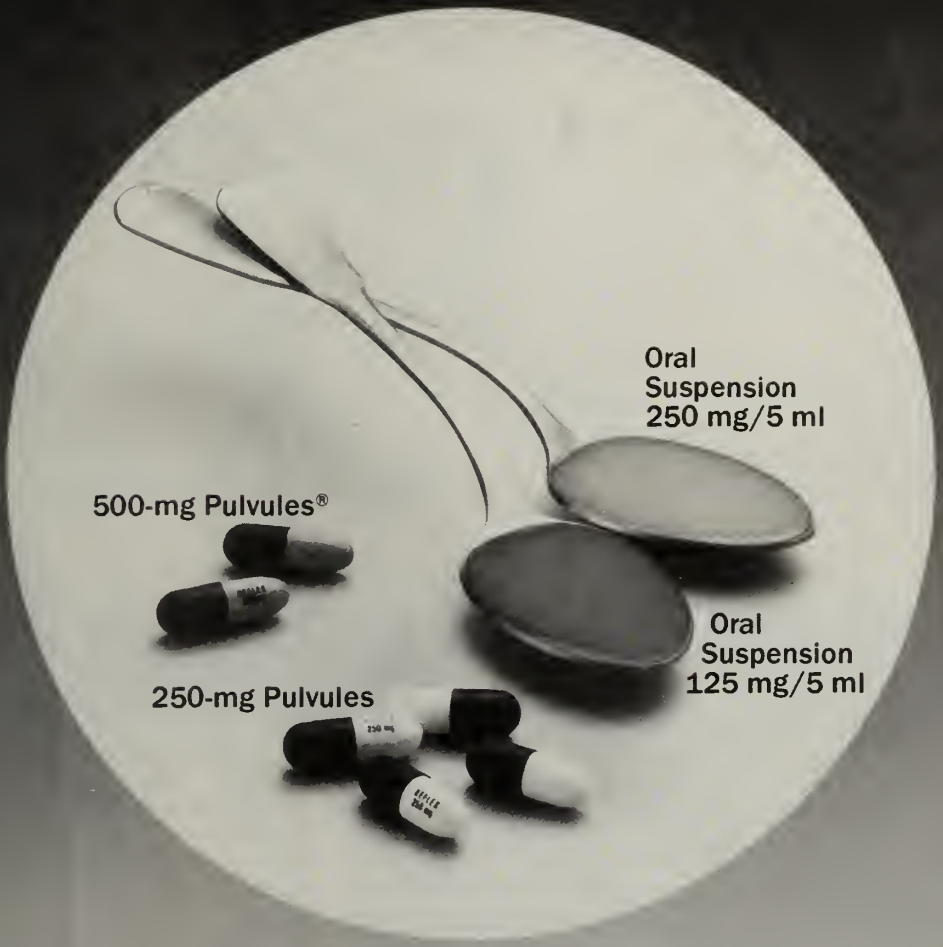

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(Continued from Page 124)

Emanuel Hospital, 2801 N Gantenbein St, Portland 97227:

Every Friday, 12:15 p.m. to 1:00 p.m. **Medical Grand Rounds.** Contact: Philippa McClure, Emanuel Hospital, 2801 N Gantenbein St, Portland 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97210:

Every Tuesday, 12:00 noon to 1:00 p.m. **Medicine Grand Rounds.** Neurological Sciences Buildings, First Floor Auditorium. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder St, Eugene 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene 97440.

Salem Hospital, 665 Winter St SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St SE, Salem 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St Vincent Hospital & Medical Center, 9205 SW Barnes Rd, Portland 97225. (503) 297-4411, Ext 2230.

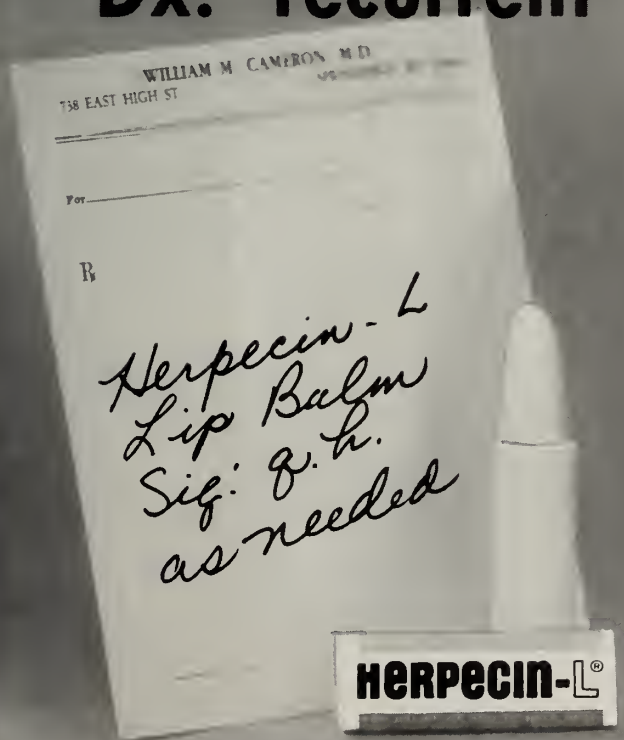
Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept of Psychiatry, Oregon Health Sciences University, Portland 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept of Medicine, Oregon Health Sciences University, Portland 97201. (503) 225-8607.

Dx: recurrent herpes labialis



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FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland 97201. (503) 225-7590.

FAMILY PRACTICE

February 9-13—**18th Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

January 23—**Infectious Disease Symposium.** Portland. Friday. OHSU Campus. Contact: OHSU-CME.

February 26-March 1—**Update in Rheumatology.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

March 2-6—**MKSAP VII Review Course.** Portland. Monday-Friday. Red Lion/Lloyd Center. Contact: OHSU-CME.

April 9-10—**Annual Alumni Meeting and Sommer Memorial Lecture Series.** Portland. Thursday-Friday. Oregon Health Sciences University. Contact: OHSU-CME.

June 26-27—**Summer Ashland Conference: Gastroenterology.** Ashland. Friday-Saturday. Windmill's Ashland Hills Inn. Contact: OHSU-CME.

July 6-11—**Summer CME at Sunriver: Plastic Surgery/Orthopedics.** Sunriver. Monday-Saturday. Sunriver Resort. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 20-22—**Pulmonary Function Testing** (Sponsor: UUMC). Tuesday-Thursday. RMCOEH, University of Utah. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

February 1-6—**Diagnostic Imaging/Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

February 9—**Stress, Emotion and Heart Disease** (Sponsor: UUMC). Monday. Westin Hotel Utah, Salt Lake City. 6 hrs. Contact: Hilmon Castle, MD, (801) 581-8664.

February 10-13—**Family Practice Refresher Course** (Sponsor: UUMC). Tuesday-Friday. Westin Hotel Utah, Salt Lake City. 28 hrs. Contact: Denise Denton, (801) 581-5224.

February 11-14—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wednesday-Saturday. Salt Lake City. 17 hrs. Contact: (801) 521-1221.

February 12-14—**Rigid Fixation Techniques/Craniomaxillofacial Surgery** (Sponsor: UUMC). Thursday-Saturday. Snowbird Resort. 20 hrs. Contact: Louis Morales, MD, (801) 581-8664.

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 19-21—**Mid-Winter Trauma Seminar for Military and Civilians** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 15 hrs. Contact: Clayton Petty, MD, (801) 581-6393.

February 20-24—**Postgraduate Course in Anesthesiology** (Sponsor: UUMC). Friday-Tuesday. Salt Lake City. 16 hrs. Contact: Theodore Stanley, MD, (801) 581-6393.

February 21-25—**Annual Ob-Gyn Update** (Sponsor: UUMC). Saturday-Wednesday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 22-27—**Park City Dermatology Seminar** (Sponsor: UUMC). Sunday-Friday. Park City. 18 hrs. Contact: Gerald Kruegar, MD, (801) 581-7837.

February 23-27—**Surgical Pathology Workshops** (Sponsor: UUMC). Monday-Friday. The Yarrow, Park City. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

February 25-28—**Gynecologic Oncology** (Sponsor: UUMC). Wednesday-Saturday. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 26-28—**Arthroscopic Surgery** (Sponsor: UUMC). Thursday-Saturday. Westin Hotel Utah, Salt Lake City. 21 hrs. Contact: Robert Metcalf, MD, (801) 581-7601.

March 2-6—**Advances in Internal Medicine.** (Sponsor: UUMC). Monday-Friday. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-7801.

March 8-13—**Diagnostic Imaging and Interventional Radiology** (Sponsor: UUMC). Sunday-Friday. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

March 9-13—**Medical and Surgical Advances in GI** (Sponsor: UUMC). Monday-Friday. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

(Continued on Page 130)

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(Continued from Page 127)

March 9-14—**Advanced Rheumatology 1987** (Sponsor: UUMC). Monday-Saturday. Snowbird Resort. 20 hrs. Contact: John Ward, MD, (801) 581-8664.

March 11-13—**9th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wednesday-Friday. Salt Lake Hilton. 14 hrs. Contact: Katharine Blosch, (801) 466-3500.

March 16-20—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Monday-Friday. Park City. 30 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 26-28—**Neurology for the Practitioner** (Sponsor: UUMC). Thursday-Saturday. Salt Lake City. 15 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

April 6-8—**Genetic Testing and New Biomedical Technologies in the Prevention of Occupational and Environmental Disease** (Sponsor: UUMC). Monday-Wednesday. Park City. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 14—**Occupational Medicine.** Seattle. Wednesday. Contact: Northwest Hospital, Education & Training Dept, 1550 N 115th St, Seattle 98133. (206) 364-0500, ext 1621.

January 15-16—**Agricultural Health and Safety.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

January 21—**Ectopic Gestations and Implementation Failures.** Seattle. Wednesday. U/W Health Sciences. Contact: U/W.

January 23—**Topics in Pulmonary Medicine: Interstitial Lung Disease.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 30—**Alternative Delivery and Financing Systems: Your Options and How to Evaluate Them.** Seattle. Friday. Contact: AMA, Dept of Practice Management, 535 N Dearborn St, Chicago, IL 60610. (312) 645-4958.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

January 31—**Management of Psychotic Patient in the Office Setting.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

February 4-6—**Spirometry Training for Worker Screening.** Seattle. Wednesday-Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

February 5-6—**Aging and the Elderly.** Seattle. Thursday-Friday. Contact: U/W.

February 6-7—**Modern Concepts in Allergy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 11—**Vocational Rehabilitation.** Bellevue. Wednesday. Contact: U/W.

February 11—**Lifestyles.** Seattle. Wednesday. Contact: Northwest Hospital, Education & Training Dept, 1550 N 115th St, Seattle 98133. (206) 364-0500, ext 1621.

February 11-13—**Vocational Rehabilitation Conference.** Seattle. Wednesday-Friday. Contact: U/W.

February 19-20—**Sexual Assault: Advances in Medical-Legal Issues.** Seattle. Thursday-Friday. Contact: Sexual Assault Center, Harborview Medical Center, 325 Ninth Ave, Seattle 98104. (206) 223-3047.

February 20-21—**Office Gynecology for the Primary Care Physician.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Health and Safety of Firefighters.** Seattle. Thursday-Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

March 13—**Recent Developments in Occupational Medicine.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

March 13—**Anxiety/New Research Findings for the Clinician.** Seattle. Friday. Westin Hotel. Contact: U/W.

March 18—**New Directions in Gynecologic Research.** Seattle. Wednesday. U/W Health Sciences. Contact: U/W.

March 20—**Neuro-Opthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

March 30-April 10—**Rehabilitation Medical Review.** Seattle. Monday-Friday. Stouffer Madison Hotel. Contact: U/W.

April 15-16 —**Introduction to Industrial Hygiene.** Seattle. Wednesday-Thursday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 17—**Basic Monitoring Laboratory.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 25—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 8—**Current Issues in Asbestos Control.** Seattle. Friday. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

June 17-19—**Family Violence.** Seattle. Wednesday-Friday. Kane Hall, U/W. Contact: U/W.

WYOMING

February 28-March 7—**Selected Topics in Wilderness and Environmental Medicine.** A nordic skiing adventure at Yellowstone National Park. One week. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. 24 hrs. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

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FAMILY PRACTICE opportunities available in New Mexico communities. Financial assistance available; excellent weather in the Sunbelt. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Room at The University of California Davis Medical Center. The University serves a large region of Northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff in addition to treating patients, primarily. Opportunities exist for involvement in other School of Medicine teaching activities. Applicants should send curriculum vitae to Robert W. Derlet, MD, University of California Davis Medical Center, 2315 Stockton Blvd., Department of Emergency Medicine, Trailer 1219, Sacramento, CA 95817.

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VASCULAR GENERAL SURGEON—To associate with senior Surgeon. Well established referral practice. Salary plus percentage. Central California. Send curriculum vitae to Number 165, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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CALIFORNIA: Openings for emergency department Medical Directors and full-time staff physicians are immediately available at two client hospitals in California. Guaranteed rate of compensation, occurrence malpractice insurance coverage, flexible scheduling, CME allowance, plus more. For additional details contact Bill Salmo, Spectrum Emergency Care, 6275 Lehman Dr., Ste. C202, Colorado Springs, CO 80918; 1 (800) 525-3681; (303) 590-1755.

OB/GYN—Excellent private practice opportunity with income guarantee in the resort community of Ruidoso, New Mexico. Please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

MEDICAL ONCOLOGY FELLOWSHIP—CALIFORNIA. Starting in July, 1988, 2 or 3 year training programs at City of Hope Medical Center in Duarte, California are available. Candidates must be board eligible in internal medicine and eligible for California licensure; Individuals with a strong interest in an expanding research program in cancer pharmacology are encouraged to apply. Inquiries should be sent to: Dr Lucille A. Leong, Dept. of Medical Oncology, 1500 E. Duarte Rd., Duarte, CA 91010, or telephone Dr Leong at (818) 359-8111.

FAMILY PRACTICE. Steinbeck Country, BC/BE FP to join dynamic group; includes hospital care, OB, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hr. to Monterey, three hrs. to S.F. Call or write: Helen Poole, 210 Canal St., King City, CA 93930; (408) 385-5471.

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STAFF PSYCHIATRISTS. Fresno County is accepting applications for two physicians to fill contract positions in Mental Health Services. Work as a psychiatric consultant on a treatment team with other professionals in a variety of outpatient and inpatient settings. California license and completion of approved psychiatric residency required. Contract salary range $62,000 to $68,000, plus extra pay for inpatient assignment, weeknight or weekend coverage (on rotation with 10 or more psychiatrists). Benefits include: 5 weeks unscheduled time (vacation, sick leave, CME) and 10 paid holidays. Send résumé and copy of California license to Robert A. Kinsey, MD, Medical Director, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 453-4024.

FAMILY PRACTICE WASHINGTON STATE OPPORTUNITIES: Join five other Family Medicine Physicians in a busy multispecialty clinic in the Pacific Northwest. First year income guarantee, malpractice and excellent benefits including Northwest lifestyle. Contact: The Friedrich Group, Inc., 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 842-5248 or (206) 633-2964.

EMERGENCY PHYSICIAN NEEDED

Tulare District Hospital seeks EM physician for permanent hospital position. Board prepared in EM, FP or IM or minimum 2 years EM experience. Competitive remuneration, malpractice paid 112 bed hospital, Level III Trauma Center. Excellent ancillary services. Located in central California's San Joaquin Valley. Superior lifestyle, excellent family environment, attractive real estate prices. Steady growth community. Interested candidates are invited to send CV to:

A. C. Jaramillo, MD, Medical Director
Emergency Services, Tulare District Hospital
869 Cherry St., Tulare, CA 93274.

OLYMPIA, WASHINGTON—Family Practitioner interested in associate. Attractive suburban setting. Salary guarantee with goal of eventual partnership. Excellent medical community in "America's Fourth Most Livable City." Send CV to Number 161, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPAEDICS—Private practice opportunity in Espanola, New Mexico. Financial assistance with income guarantee. Easy access to all forms of recreation—only 20 miles north of Santa Fe. For further information, please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

OTOLARYNGOLOGIST: BC/BE and also interested in facial plastics to join 20 physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OB/GYN: Multispecialty group in Northwest Washington desires second obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administration, 1400 E. Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

BOARDED FAMILY PHYSICIAN to associate with established FP, obstetrics preferable, small practice gives opportunity for individualized care. Escondido Family Practice, 705 E. Ohio Ave., Escondido, CA 92025.

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Director/Physician Recruitment
CIGNA Healthplans of California
505 N. Brand Blvd., Suite 400-49
Glendale, CA 91203

PHYSICIANS WANTED

ANESTHESIOLOGIST sought for the Espanola Hospital in Espanola, New Mexico. Financial assistance/income guarantee. For further information please submit CV to: Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or, call 1 (800) 545-4030, Ext. 8300.

BC/BE FAMILY PRACTITIONER is needed immediately to join, with the option of buying out, a very busy 30-year established private practice in Southeast New Mexico with a population of 14,000. Great place to raise a family—peaceful community with year-round recreation. Excellent weather; excellent school system. Fully-equipped, new 38 bed hospital. Financial package negotiable. Forward CV to: Professional Medical Office Building, Ste. D, 612 N. 13th St., Artesia, NM 88210.

NORTHERN SAN FRANCISCO BAY AREA. Seeking physician Board certified or eligible in Internal Medicine for Internist position in growing department of medicine. Competitive salary and excellent benefits. Call or write: Chief, Department of Medicine, Kaiser Permanente Medical Center, 1550 Gateway Blvd., Fairfield, CA 94533; phone (707) 427-4200.

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A State Application (Form 100-678) must be received between January 5 and February 5, 1987. Any postmarked after that date will not be accepted. All applications will be screened and only those qualified will be allowed to participate in the oral examination. Send applications to: Department of Consumer Affairs, 1020 N Street, Exam Unit, Room 537, Sacramento, CA 95814. Telephone: (916) 324-1699.

SAN FRANCISCO BAY AREA. Family Practitioner, Board-eligible or Board-certified, to join large multispecialty, prepaid group practice. Excellent fringe benefits. Superb environment. Contact James Conroy, MD, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119. Telephone (408) 972-3276. Or call collect to (408) 972-3000.

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Tulare District Hospital seeks Board certified/eligible Otolaryngologist for excellent private practice opportunity. Financial incentives, guaranteed income. 75,000 service area population. Located in central California's San Joaquin Valley, Tulare offers excellent family environment, superior lifestyle and attractive real estate prices. Steady growth community. Proven income potential. Interested candidates are invited to send CV or call:

Tulare District Hospital, Physician Recruiting
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(213) 216-2687.

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INTERNIST—BC or BE. Excellent professional opportunity to join active solo practice with good possibility of full partnership. Desirable location in San Jose, California with excellent hospital facilities. Send CV and letter of introduction to PO Box 1833, Campbell, CA 95008.

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PHYSICIANS WANTED

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GENERAL INTERNAL MEDICINE with emphasis on Cardiology. Multispecialty clinic in prime urban location in Washington. First year income guarantee and excellent benefits including Pacific Northwest lifestyle. Send CV or call: The Friedrich Group, Inc., 9284 Ferncliff NE, Bainbridge Island, WA 98110; (206) 842-5248 or (206) 633-2964.

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BEAUTIFUL MOUNTAIN SETTING—BC/BE General Internist needed in rapidly expanding, thriving internal medicine practice in northwest Montana. Wide range of clinical opportunities offered with virtually unlimited recreational opportunities including skiing, hiking, fishing in immediate wilderness surroundings. Send CV to Dr Robert Patton, 418 Maine Ave., Libby, MT 59923; (406) 293-7758.

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BOARD CERTIFIED INTERNIST to join busy solo internist in General Internal Medicine practice. Salary leading to partnership. Academic appointment available. Send CV to William B. A. Bentley, MD, 901 Rancho Ln, Las Vegas, NV 89102.

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PHYSICIANS WANTED

SAN DIEGO, CALIFORNIA—Live and work in America's finest city. Career opportunities for full-time Family Practitioners and Internists. Send CV in confidence to Medical Director, Mercy Care-Point Medical Group, 681 Encinitas Blvd., Suite 406-G, Encinitas, CA 92024.

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INTERNAL MEDICINE/CARDIOLOGY PRACTICE available 1987. Office association with two Cardiologists. Salt Lake City. Send résumé to Number 1, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FOR SALE: SAN MATEO, CALIFORNIA. Established General Practice—retiring. Accounts, equipment, furniture. Terms. Reply to Number 2, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1987: Date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 18-20, 1986, Snowmass.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1986, Westin Ilikai Hotel, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1987: Date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 2-4, 1986, Holiday Inn, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1987: Date and place to be announced.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 10-12, 1986, Yarrow Holiday Inn, Park City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 623-4801. Annual Meeting: September 18-21, 1986, Spokane.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1987: Date and place to be announced.

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Rocephin® IV·IM ROCHE®
ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

MICROBIOLOGY The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and *in* clinical infections (see Indications and Usage)

GRAM-NEGATIVE AEROBES Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, e g , penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

GRAM-POSITIVE AEROBES Staphylococcus aureus (including penicillinase producing strains) and *Staphylococcus epidermidis* (Note methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta-hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

GRAM-NEGATIVE AEROBES Citrobacter freundii, Citrobacter diversus, Providencia species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*

ANAEROBES Bacteroides species, *Clostridium* species (Note most strains of *C difficile* are resistant)

SUSCEPTIBILITY TESTING Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, Am *J Clin Pathol* 45 493 496, 1966, Standardized Disk Susceptibility Test, *Federal Register* 39 19182-19184, 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

DILUTION TECHNIQUES Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g , urine), in which high antibiotic levels are attained

E coli ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

PROPHYLAXIS The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

ROCEPHIN™ (ceftriaxone sodium/Roche)

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS – pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY – rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC – eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL – diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC – elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL – elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM – headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY – moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS – diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis

DOSAGE AND ADMINISTRATION Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g , dialysis patients) and in patients with both renal and hepatic dysfunctions

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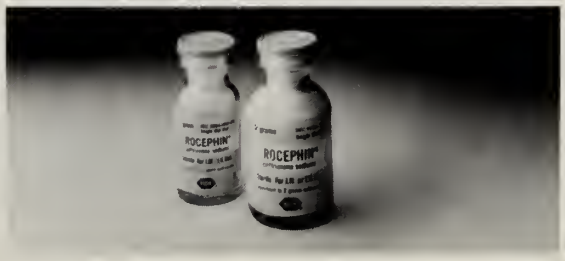

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Please see adjacent page for references and summary of product information.

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The Western Journal of Medicine

VOLUME 146 • NUMBER 2 FEBRUARY 1987

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Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase, and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.
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SINCE 1902 ISSN 0093-0415

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Advertisements—The journal is published the first week of the month. Advertising copy must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. *The journal reserves the right to reject any advertisement.*

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The subscription price per year is $30 in the United States and Canada (US funds); $50 in all other countries. Single copies are $4.50 (which includes postage and handling). Address all subscription communications to:
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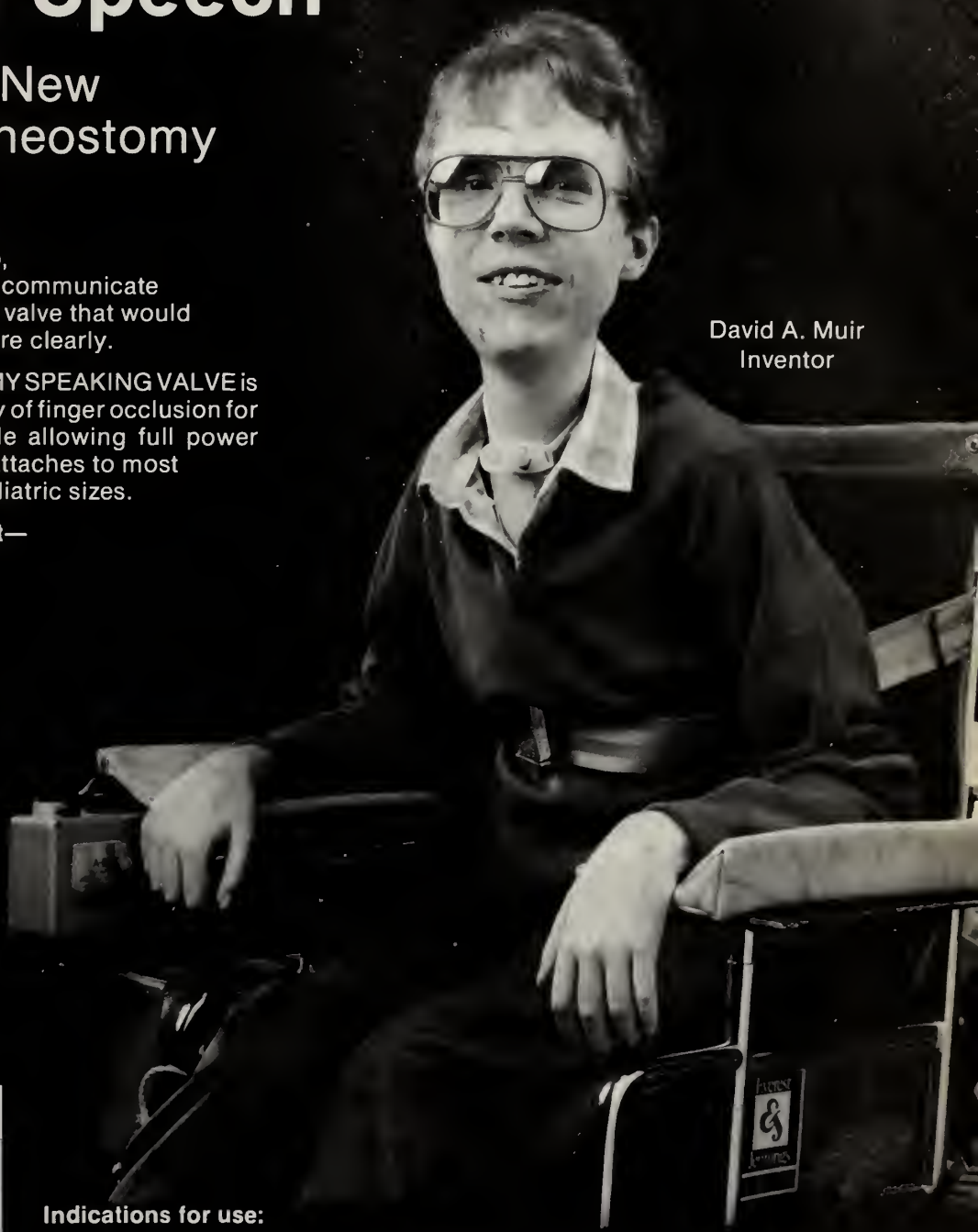

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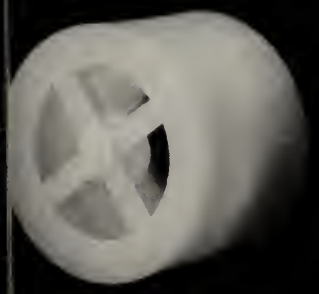

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Comparison of Adverse Effects for CAPOTEN (≤ 100 mg) versus Placebo in Hypertensive Patients with Normal Renal Function (N = 1,622)‡[2]

ADVERSE EFFECT	CAPOTEN (N=1,174) (% affected)	Placebo (N=448) (% affected)
Headache	5.2	6.9
Rash	3.7	2.5
Dizziness	3.5	2.0
Nausea	3.2	2.0
Fatigue	3.1	2.0
Taste alteration	1.5	1.1
Gastrointestinal	1.4	0.7
Diarrhea	1.1	1.1

‡None of the differences between captopril and placebo was statistically significant. For the most part, adverse effects were mild and transient and usually did not require discontinuation of therapy. Only 5.5% of the patients in this data base discontinued because of an adverse effect. Data include adverse effects for CAPOTEN with an incidence greater than 1%.

†CAPOTEN may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine < 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658D)

References:

1. PDS Alpha, *National Prescription Report,* Pharmaceutical Data Services, Subsidiary of McKesson Corporation.
2. Data on file, Squibb Institute for Medical Research.

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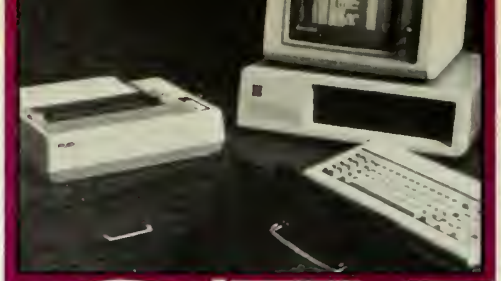

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★ **Official Journal of the Arizona Medical Association, the California Medical Association, the Idaho Medical Association, the Montana Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society. Affiliated Specialty Society: California Society of Internal Medicine.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MDTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MDTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MDTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MDTRIN; use with caution in patients with a history of cardiac decompensation or hypertension.

MDTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MDTRIN is added.

The antipyretic, anti-inflammatory activity of MDTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGDT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MDTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MDTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MDTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MDTRIN and coumarin.

Pregnancy and nursing mothers: MDTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MDTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIDNS).

Incidence less than 1% Probable Causal Relationship*

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIDNS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIDNS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CDNTRAINDICATIDNS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown*

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MDTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

HERNIA REPAIR WITHOUT DISABILITY—Second Edition—Irving L. Lichtenstein, MD, Fellow, American College of Surgeons, International College of Surgeons and American Association for the Advancement of Science; Diplomate, American Board of Surgery, Pan American Medical Association and National Board of Medical Examiners; Associate, World Medical Association; Founder and Director of the Lichtenstein Hernia Institute. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Ct, St Louis, MO 63043, 1986. 250 pages, $85.

INSIDE DOCTORING—STAGES AND OUTCOMES IN THE PROFESSIONAL DEVELOPMENT OF PHYSICIANS—Edited by Robert H. Coombs, PhD, Professor and Director, Office of Education, Neuropsychiatric Institute; D. Scott May, MD, NIMH Research Fellow, Department of Psychiatry, and Gary W. Small, MD, Assistant Professor of Psychiatry, UCLA School of Medicine, Los Angeles. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 289 pages; $39.95, $14.95 (paperback).

INTRODUCTION TO DIAGNOSTIC IMAGING—Edited by Lee Sider, MD, Assistant Professor of Radiology, Northwestern University Medical School, and Director, Medical Student Education, Northwestern Memorial Hospital, Chicago. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 290 pages, $29.50 (paperback).

MANAGEMENT OF HYPERTENSION—Norman M. Kaplan, MD, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas. Creative Infomatics, Inc, PO Box 1607, Durant, OK 74702-1607, 1986. 159 pages (paperback), no price given.

MANAGEMENT OF SPINAL CORD INJURIES—Edited by Ralph F. Bloch, MD, PhD, FRCP(C), Associate Professor of Medicine, McMaster University Faculty of Health Sciences, and Director of Neurotrauma Program, Chedoke Rehabilitation Centre, and Mel Basbaum, MSW, Social Work Department, Chedoke-McMaster Hospital, Chedoke Rehabilitation Centre, Hamilton, Ontario, Canada. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1986. 447 pages, $53.50.

PATHOLOGY OF THE TESTIS AND ITS ADNEXA—Volume 7 in CONTEMPORARY ISSUES IN SURGICAL PATHOLOGY—Edited by Aleksander Talerman, MD, PhD, FRCPath, Professor of Pathology and Obstetrics and Gynecology, University of Chicago Pritzker School of Medicine, Chicago, and Lawrence M. Roth, MD, Professor of Pathology and Director, Division of Surgical Pathology, Indiana University School of Medicine, Indianapolis. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 255 pages, $50.

PERSONAL MONEY MANAGEMENT FOR PHYSICIANS—Fourth Edition—Lawrence Farber. Medical Economics Books, 680 Kinderkamack RD, Oradell, NJ 07649, 1986. 273 pages, $27.95.

PHYSICIAN ASSISTANTS—PRESENT AND FUTURE MODELS OF UTILIZATION—Edited by Sarah F. Zarbock, PA-C, Bone Marrow Transplant Team, Children's Hospital of Philadelphia, and Kenneth Harbert, PA-C, Manager, Physician Extenders, Geisinger Medical Center, Danville, Pennsylvania. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 138 pages, $35.

POCKET REFERENCE FOR MEDICAL INTENSIVE CARE—Barbara Anne Phillips, MD, Assistant Professor, Department of Medicine, Pulmonary Division, University of Kentucky College of Medicine, Lexington, and Director, Intensive Care Unit, Albert B. Chandler Medical Center. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850. 387 pages, $23.50 (paperback).

PRINCIPLES OF ELECTROCARDIOGRAPHY—12th Edition—Mervin J. Goldman, MD, Clinical Professor of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94023, 1986. 450 pages, $19 (paperback).

PROLACTINOMAS—Volume 2 in CONTEMPORARY ISSUES IN ENDOCRINOLOGY AND METABOLISM—Edited by Jerrold M. Olefsky, MD, Professor of Medicine, Department of Medicine / Endocrinology and Metabolism, University of California, San Diego, School of Medicine, and Veterans Administration Medical Center, La Jolla, Calif, and Richard J. Robbins, MD, Assistant Professor of Medicine, Section of Neuroendocrinology, Yale University School of Medicine, New Haven, Conn. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 223 pages, $36.

PSYCHOVENEREOLOGY—PERSONALITY AND LIFESTYLE FACTORS IN SEXUALLY TRANSMITTED DISEASES IN HOMOSEXUAL MEN—Volume 3 in Sexual Medicine—Michael W. Ross, AIDS Coordinator of the South Australian Health Commission and Senior Lecturer in Psychiatry and Community Medicine, Flinders University Medical School, Adelaide, Australia. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1986. 241 pages, $37.95.

RADIOLOGY OF ADVERSE REACTIONS TO DRUGS AND TOXIC HAZARDS—George Ansell, MD, DMRD, FRCP, FRCR, Consultant Radiologist in Charge, Whiston Hospital, Merseyside, and Lecturer in Radiodiagnosis, University of Liverpool, England. Aspen Publishers Inc, 1600 Research Blvd, Rockville, MD 20850, 1985. 357 pages, $40.

RADIONUCLIDE IMAGING OF THE GI TRACT—Volume 2 In CONTEMPORARY ISSUES IN NUCLEAR IMAGING—Edited by Fred A. Mettler, Jr, MD, Professor and Interim Chairman, Department of Radiology, University of New Mexico School of Medicine, and Chief, Radiology Service, Veterans Administration Medical Center, Albuquerque. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 345 pages, $50.

RECENT ADVANCES IN PLASTIC SURGERY—Number Three—Edited by Ian T. Jackson, FRCS, Chief, Plastic Surgery, Mayo Clinic, and Professor of Plastic Surgery, Mayo Medical School, Rochester, Minn, and Brian C. Sommerlad, MD, FRCS (Eng), Consultant Plastic Surgeon, The London Hospital, Whitechapel, London, and St Andrew's Hospital, Billericay, Essex, England. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 232 pages, $59.

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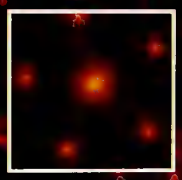

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*For a complete discussion of **CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS,** and **WARNINGS,** including avoidance of abrupt withdrawal, please see the brief summary of prescribing information on the last page of this advertisement.

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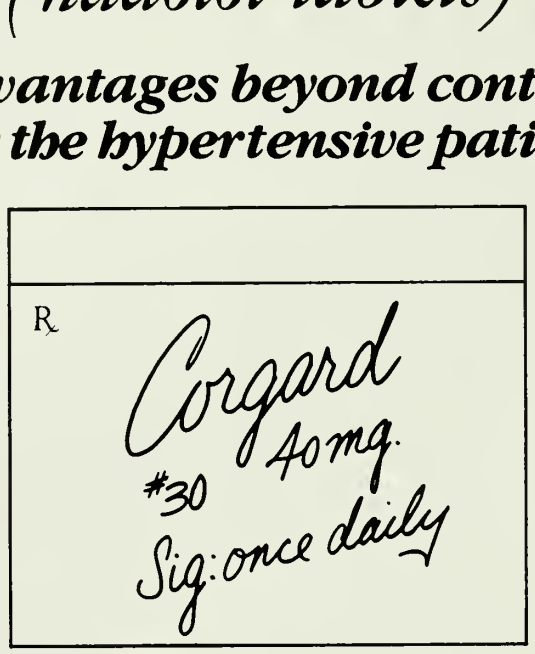
Advantages beyond control for the hypertensive patient



CORGARD® TABLETS
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DESCRIPTION: CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicology studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryocidal and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurred commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 6 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling, weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established: **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

References: 1. Alexander JC, Christie MH, Vernam KA, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984.

PRINCETON PHARMACEUTICAL PRODUCTS
A SQUIBB COMPANY

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517-532

Issued January 86

CONFIRMED

CONFIRMED BY CLINICAL EVIDENCE

ZANTAC® 150 h.s.

ranitidine HCl/Glaxo 150 mg tablets

EFFECTIVE MAINTENANCE THERAPY

for healed duodenal ulcer patients

CONFIRMED

In two randomized, double-blind, and well-controlled clinical trials, ZANTAC 150 mg h.s. significantly superior to cimetidine 400 mg h.s. for maintenance therapy in healed duodenal ulcers.

Percent of patients with observed duodenal ulcer recurrence

		0-4 months	0-8 months	0-12 months	No. patients
USA[1]	ranitidine 150 mg h.s.	9%	14%*	16%†	60
	cimetidine 400 mg h.s.	23%	34%	43%	66
UK, Ireland, Australia[2]	ranitidine 150 mg h.s.	8%‡	14%‡	23%‡	243
	cimetidine 400 mg h.s.	21%	34%	37%	241

*p=0.02
†p=0.01
‡p≤0.004
%=life-table estimates
All patients were permitted prn antacids for relief of pain.

These two trials used the currently recommended dosing regimen of cimetidine (400 mg h.s.) and ranitidine (150 mg h.s.). A comparison of other dosing regimens has not been studied.

The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.

The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Convenient once-a-night dose with a

low incidence of side effects[3]

Headache, sometimes severe, seems to be related to ranitidine administration. Other side effects have been reported; for a complete listing, see the **ADVERSE REACTIONS** section in the Brief Summary.

No significant interference with the hepatic cytochrome

P-450 enzyme system at recommended doses

ZANTAC 150 mg has no significant drug interactions with theophylline, phenytoin, or warfarin. The bioavailability of certain medications whose absorption is dependent on a low gastric pH may be altered when ZANTAC or other medications that decrease gastric acidity are administered.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets

One tablet at bedtime
for maintenance

See next page for references and
Brief Summary of Product Information.

Glaxo/ ROCHE®

CONFIRMED

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets

One tablet at bedtime for maintenance therapy in healed duodenal ulcer patients

References:

1. Silvis SE, Griffin J, Hardin R, et al: Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487.
2. Gough KR, Korman MG, Bardhan KD, et al: Ranitidine and cimetidine in prevention of duodenal ulcer relapse: A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984;ii:659-662.
3. Data available on request, Glaxo Inc.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)
ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

In active duodenal ulcer, active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Although recommended doses of ZANTAC do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Lack of experience to date precludes recommending ZANTAC for use in children or pregnant patients. Since ZANTAC is secreted in human milk, caution should be exercised when administered to a nursing mother.

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to ZANTAC® administration. Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, premature ventricular beats, and arthralgias. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients.

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

There have been rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia, and pancytopenia.

Although controlled studies have shown no antiandrogenic activity, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

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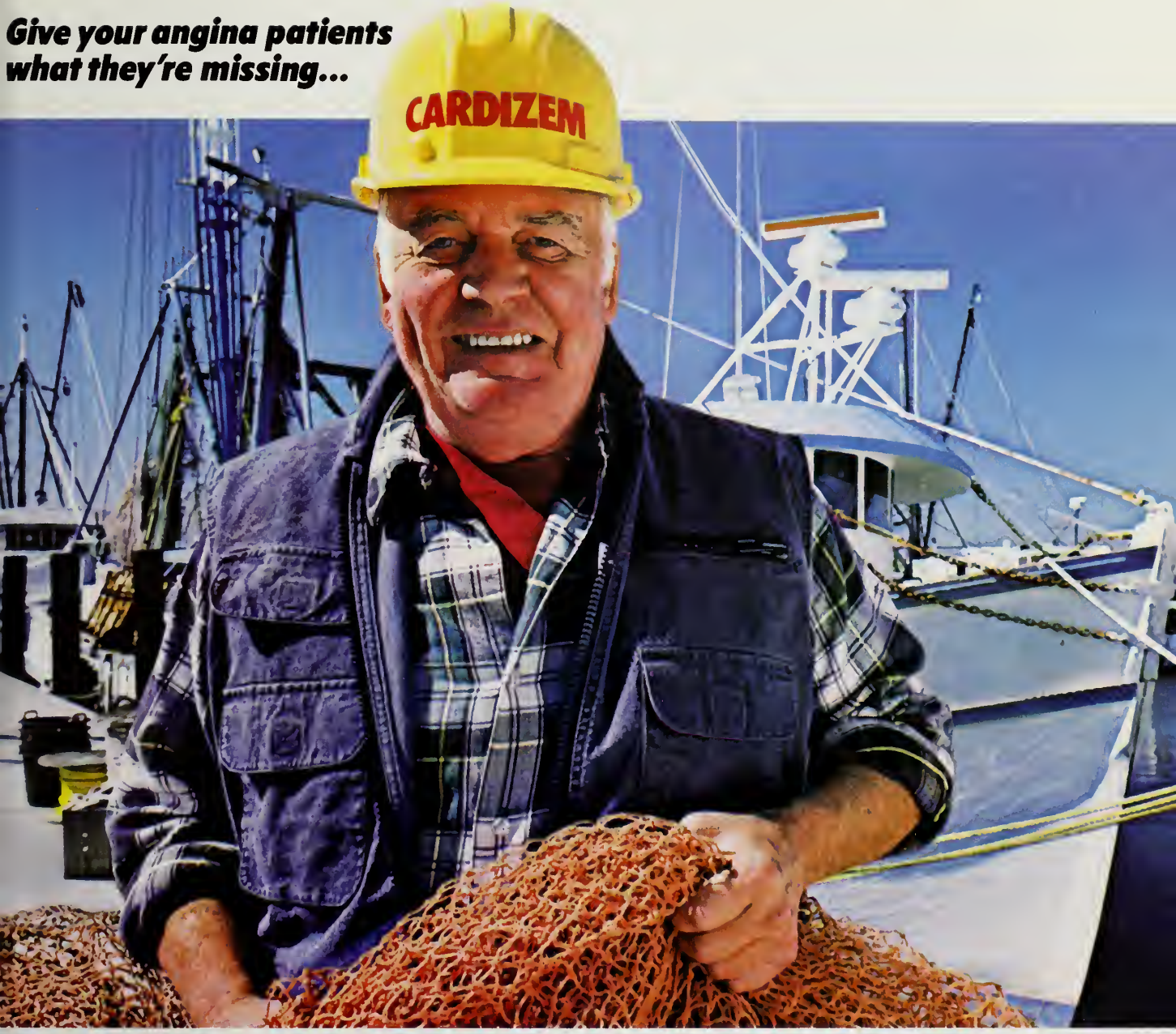
Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

Give your angina patients what they're missing...



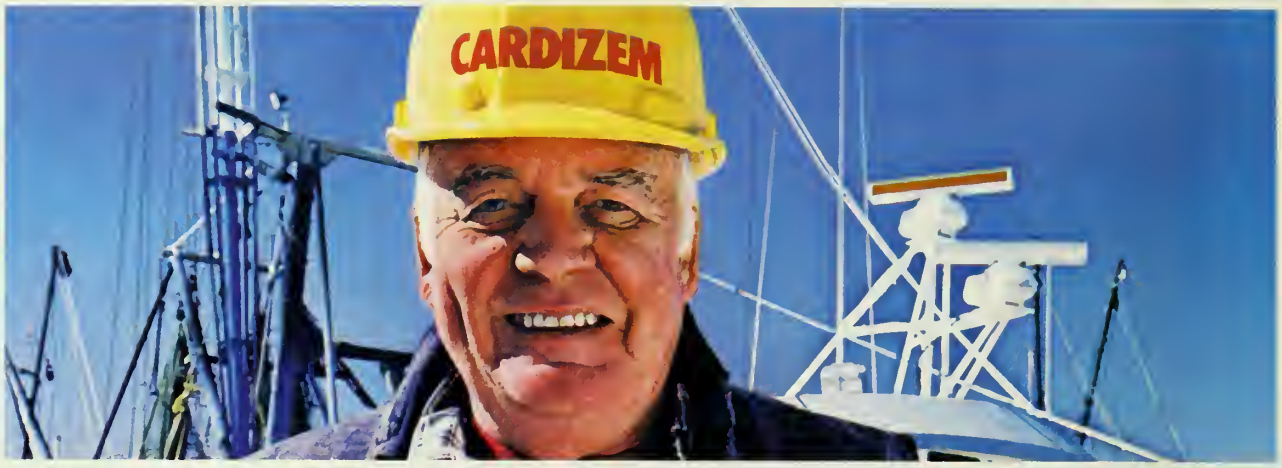
CARDIZEM®: FEW SIDE EFFECTS

diltiazem HCl/Marion

- ***Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate***
- ***Proven efficacy when used alone in angina[1]***
- ***Compatible with other antianginals[2,3]****
- ***A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD[4,5]***

****See Warnings and Precautions.***

Please see brief summary of prescribing information on the next page.



CARDIZEM® FEW SIDE EFFECTS IN ANTIANGINAL THERAPY

diltiazem HCl/Marion

60 mg tid or qid

Brief Summary
Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.
Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)
Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.
Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.
Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.
Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.
In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.
The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.
Issued 7/86
See complete Professional Use Information before prescribing.

References: 1. Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347. **2.** Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159. **3.** Johnston DL, Lesowoy R, Human DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985,55:680-687. **4.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **5.** Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50(Sept):94-116.

Another patient benefit product from
PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

0246M6

Your prescription now...

for a lifetime of happy dental visits

During the first months of life, Vi-Flor® vitamin-fluoride supplements begin to enhance tooth morphology,[1] increase enamel hardness, and promote mineralization of unerupted teeth[2]—all while providing recommended minimum daily amounts of selected vitamins.

Fluoride supplementation is both prophylactic *and* therapeutic, especially with newborns who are already in the process of developing 20 primary and 32 permanent teeth. In fact, receiving adequate systemic fluoride beginning the first months of life can help reduce childhood cavities by 50-80%.[3]

And that *daily* use through age 16 results in optimal levels of fluoride supplementation, for a lifetime of stronger teeth and lower-cost dental care.

Prescribe
Vi-Flor® vitamin-fluoride supplements...now.
The essential first step begins with you, and...

TRI·VI·FLOR®
POLY·VI·FLOR®

References:

1. Moss SJ: The worldwide decline in caries prevention, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 2.

2. Newbrun E: How fluoride works: Topical vs. systemic action, in Mead Johnson Clinical Report Series, Clinical Importance of Fluoride Nutrition in Infants, Children, and Young Adults. Chicago, Pragmaton® 1985, Number 1, p. 5.

3. Aasenden R and Peebles T: Effects of fluoride supplementation from birth on human deciduous and permanent teeth. *Arch Oral Biol* 1974;19:321.

Mead Johnson
NUTRITIONAL DIVISION

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L-K244-1-87

Routine VI-FLOR® supplementation

to help you guard appropriate patients against caries risk and nutritional risk.

INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR® with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:
Supplemental Fluoride Dosage Schedule (mg/day)*

Age	Concentration of Fluoride in Drinking Water (ppm)		
	<0.3	0.3-0.7	>0.7
2-wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule. *Pediatrics* 63(1):150-152, 1979.
**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.25 mg with Iron	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

REFERENCES:
1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. *J Dentistry for Children* 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. *Pharmacology and Therapeutics in Dentistry* 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. *J Pediatrics* 80:1018-1021 (June) 1972.

VI-SOL®/VI-FLOR® products are the nation's most prescribed children's vitamin and vitamin-fluoride supplements.

(For complete details, please consult full prescribing information.)

Mead Johnson
NUTRITIONAL DIVISION

In Memoriam

California Medical Association

DEVINE, SHERMAN S., Sacramento. Died Aug 26, 1986, aged 78. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1944. Licensed in California in 1945. Dr Devine was a member of the Sacramento-El Dorado Medical Society.

❧

DOWLING, WILLIAM F., San Francisco. Died Jul 29, 1986, aged 61. Graduate of St Louis University School of Medicine, 1949. Licensed in California in 1950. Dr Dowling was a member of the San Francisco Medical Society.

❧

DOZIER, DAVID F., Sr, Sacramento. Died Sep 16, 1986, aged 87. Graduate of Stanford University, Stanford, California, 1926. Licensed in California in 1926. Dr Dozier was a member of the Sacramento-El Dorado Medical Society.

❧

EVANS, LELAND M., Los Angeles. Died Sep 29, 1986, aged 88. Graduate of George Washington University, Washington, DC, 1925. Licensed in California in 1926. Dr Evans was a member of the Los Angeles County Medical Association.

❧

FLANDERS, JACKSON, Los Gatos. Died Jul 14, 1986, aged 84. Graduate of Harvard Medical School, 1929. Licensed in California in 1946. Dr Flanders was a member of the San Mateo County Medical Society.

❧

GIFFORD, BYRON L., Santa Barbara. Died Sep 27, 1986, aged 80. Graduate of University of Minnesota, 1932. Licensed in California in 1947. Dr Gifford was a member of the Santa Barbara County Medical Society.

❧

GILMAN, PHILIP K., Watsonville. Died Sep 25, 1986, aged 77. Graduate of University of Rochester School of Medicine, Rochester, New York, 1935. Licensed in California in 1936. Dr Gilman was a member of the Santa Cruz County Medical Society.

❧

HUME, PORTIA BELL, St Helena. Died Aug 2, 1986, aged 85. Graduate of University of California, San Francisco, School of Medicine, 1938. Licensed in California in 1938. Dr Hume was a member of the Napa County Medical Society.

❧

JAKES, WAYNE ELLIOT, Santa Barbara. Died Jul 31, 1986, aged 39. Graduate of Northwestern University Medical School, Chicago, 1973. Licensed in California in 1977. Dr Jakes was a member of the Santa Barbara County Medical Society.

❧

KASTNER, SCOTT M., Chico. Died Aug 23, 1986, aged 36. Graduate of Jefferson University, Philadelphia, 1976. Licensed in California in 1978. Dr Kastner was a member of the Butte-Glen Medical Society.

❧

KESSLER, ERNEST E., Glendale. Died Aug 23, 1986, aged 93. Graduate of USC School of Medicine, Los Angeles, 1918. Licensed in California in 1918. Dr Kessler was a member of the Los Angeles County Medical Association.

❧

LINDNER, HAROLD H., San Francisco. Died Jul 27, 1986, aged 74. Graduate of University of California, San Francisco, School of Medicine, 1933. Licensed in California in 1933. Dr Lindner was a member of the San Francisco Medical Society.

LYONS, DOROTHY J., Los Angeles. Died Sep 19, 1986, aged 75. Graduate of Medical College of Pennsylvania, Philadelphia, 1945. Licensed in California in 1947. Dr Lyons was a member of the Los Angeles County Medical Association.

❧

MCCAULEY, JOHN J., Hemet. Died Jul 4, 1986, aged 74. Graduate of Georgetown University School of Medicine, Washington, DC, 1950. Licensed in California in 1952. Dr McCauley was a member of the Riverside County Medical Association.

❧

MCKEEHAN, HAROLD L., South Gate. Died Sep 2, 1986, aged 65. Graduate of Creighton University School of Medicine, Omaha, 1944. Licensed in California in 1945. Dr McKeehan was a member of the Los Angeles County Medical Association.

❧

MESSENGER, HAROLD M., San Diego. Died Sep 3, 1986, aged 73. Graduate of Ohio State University, 1939. Licensed in California in 1948. Dr Messenger wasa member of the San Diego County Medical Society.

❧

MORRIS, KATHLEEN G., Petaluma. Died Oct 26, 1986, aged 82. Graduate of University of California, San Francisco, School of Medicine, 1930. Licensed in California in 1930. Dr Morris was a member of the Sonoma County Medical Association.

❧

NORTHRUP, JUDY W., San Francisco. Died Aug 25, 1986, aged 45. Graduate of Ohio State University College of Medicine, Columbus, 1966. Licensed in California in 1977. Dr Northrup was a member of the San Francisco Medical Society.

❧

OLIEDO, GEORGE FRANCIS, Marysville. Died Sep 21, 1986, aged 90. Graduate of University of California, San Francisco, 1923. Licensed in California in 1923. Dr Oliedo was a member of the San Francisco Medical Society.

❧

PALM, REBA DELPHINE, Vallejo. Died Aug 24, 1986, aged 71. Graduate of University of Texas, 1942. Licensed in California in 1944. Dr Palm was a member of the Solano County Medical Society.

❧

RITCHEY, CHARLES L., Hayward. Died Aug 26, 1986, aged 51. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1959. Licensed in California in 1960. Dr Ritchey was a member of the Alameda-Contra Costa Medical Association.

❧

ROCHEX, FRANCIS J., San Francisco. Died Aug 28, 1986, aged 85. Graduate of University of California, San Francisco, 1928. Licensed in California in 1928. Dr Rochex was a member of the San Francisco Medical Society.

❧

SCHAUPP, JOHN B., San Francisco. Died Sep 13, 1986, aged 68. Graduate of Stanford University, Stanford, California, 1944. Licensed in California in 1944. Dr Schaupp was a member of the San Francisco Medical Society.

❧

SCHONBERG, STEPHEN S., Thousand Oaks. Died Jul 6, 1986, aged 48. Graduate of Columbia University College of Physicians and Surgeons, New York, 1963. Licensed in California in 1969. Dr Schonberg was a member of the Ventura County Medical Society.

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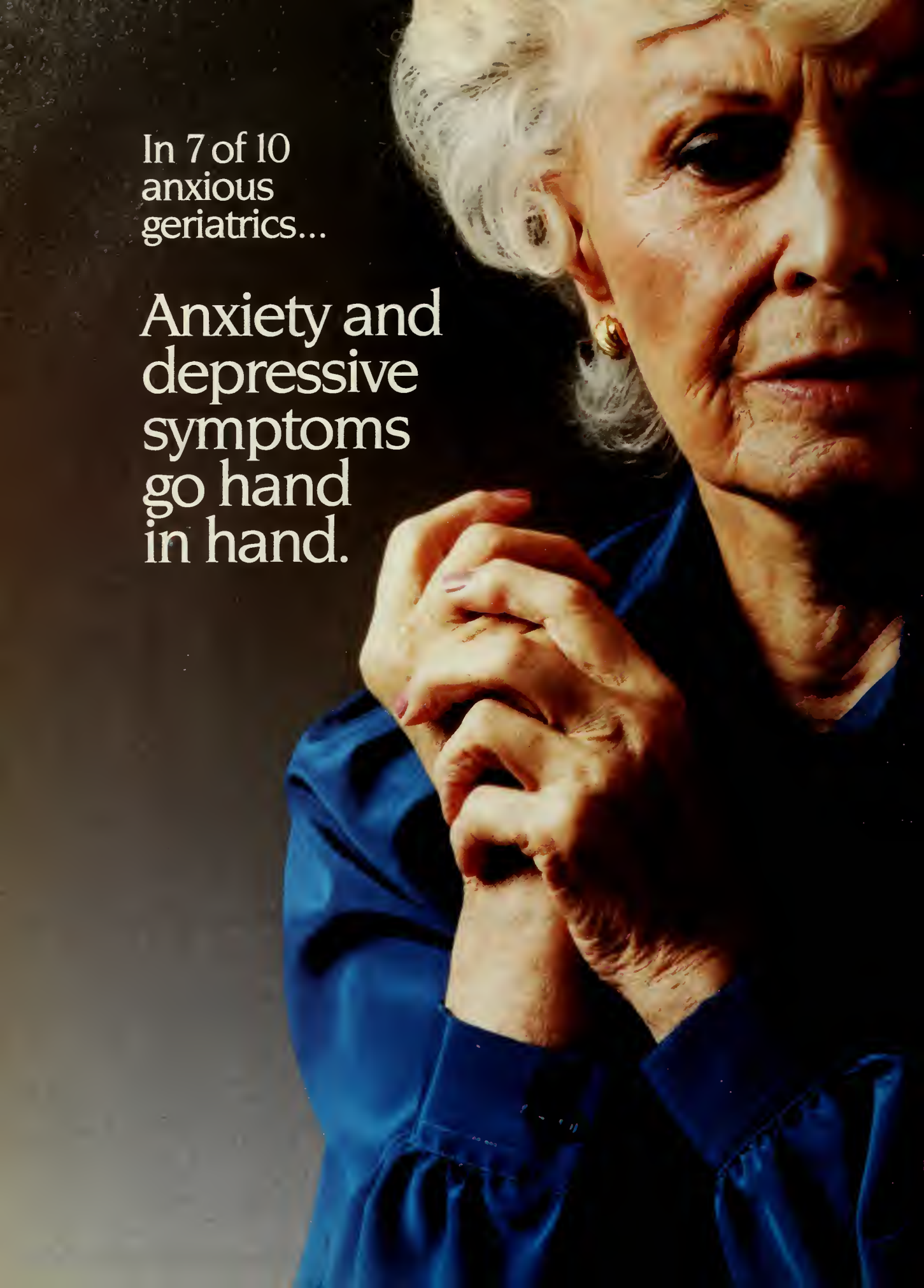
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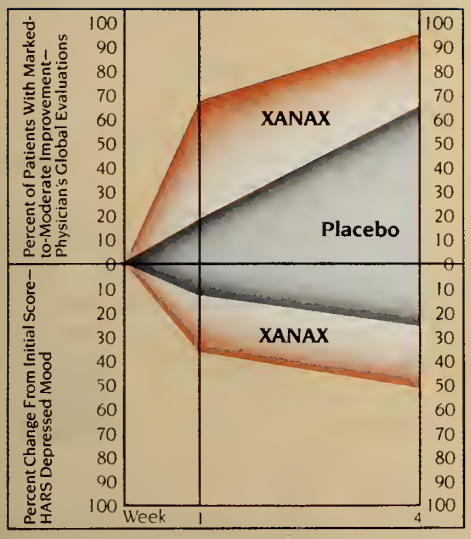

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1 Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984 35(1):100–112

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Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

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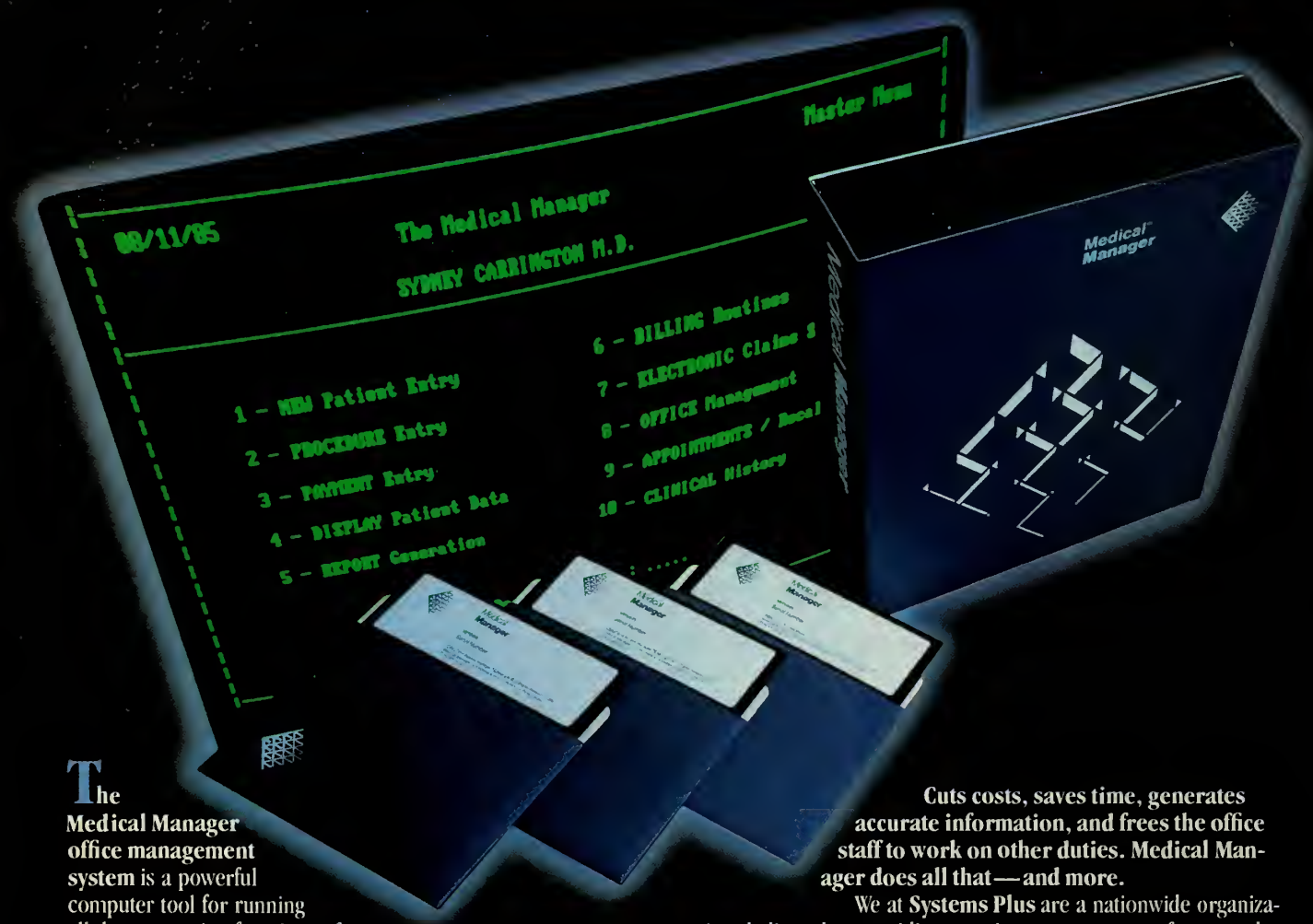

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ARIZONA

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 18—**Current Perspectives: Lipids.** Arizona Medical Association, Phoenix. Wed. Contact: ArMA.

February 18-21—**Crises and Controversies in Pediatrics.** Doubletree Inn, Tucson. Wed-Sat. Contact: U of A.

February 19—**First Annual Interventional Angiography Symposium.** Thurs. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

February 19-21—**Frontiers in Ophthalmology.** Thurs-Sat. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

February 22-25—**First Annual Barrow Neurological Institute Magnetic Resonance Imaging Conference.** Mountain Shadows Resort, Scottsdale. Sun-Wed. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

February 25-27—**Tenth Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton, Scottsdale. Wed-Fri. Contact: Maricopa Medical Center, (602) 267-5444.

February 26-28—**Neurology and Neurosurgery of the Aging.** Mountain Shadows Resort, Scottsdale. Thurs-Sat. Contact: Barrow Neurological Institute, (602) 285-3178 or (800) BARROW1.

March 4-8—**11th Annual Valley of the Sun Dermatologic Symposium.** Loews Paradise Valley Resort, Scottsdale. Wed-Sun. Contact: Millard Thaler, MD, 2055 E Southern, #B, Tempe 85282.

March 7—**Rehabilitation in the Aging: 2nd Annual Update.** Westward Look Resort, Tucson. Sat. Contact: U of A.

March 11—**Current Perspectives: Lipids.** Pima County Medical Society Building, Tucson. Wed. Contact: ArMA.

March 11-13—**Them Ol' Bones.** Wed-Fri. Contact: Christine Campbell for St Luke's Medical Center, (602) 947-7756.

March 17-20—**Pediatric Update—1987.** La Posada Resort, Scottsdale. Tues-Fri. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 19-21—**23rd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thurs-Sat. Contact: Sandy Younker-Hellman, RN, U of A, (602) 327-5461.

March 19-21—**Gastroenterology for Clinicians.** Scottsdale. Thurs-Sat. Contact: Jeanne Sun Harris, 4129 E Sandy Mt Rd, Scottsdale 85253.

March 21-22—**13th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Sat-Sun. Contact: Maricopa Medical Center, (602) 267-5371.

March 31-April 3—**12th Annual Update: Primary Care.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: U of A.

April 6-8—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Mon-Wed. Contact: American College of Cardiology, (301) 897-5400, ext 226.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

April 22—**Current Perspectives: Wellness.** Arizona Medical Association, Phoenix. Wed. Contact: ArMA.

April 23—**Current Perspectives: Wellness.** VA Medical Center, Prescott. Thurs. Contact: ArMA.

April 24—**Clinical Aspect of Aging.** Fri. Contact: Dr Stonefeld, (602) 230-3479.

May 9-10—**Pathology of AIDS.** Loews Ventana Canyon Resort, Tucson. Sat-Sun. Contact: Beverly Richter for Arizona Society of Pathologists, (602) 246-8901.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

March 18-21—**10th Annual Course: Frontiers in Allergy and Asthma—A Comprehensive Update for the Treatment of Allergy/Asthma Patients.** UCD at Embassy Suites, Napa Valley. Wed-Sat. 17 hrs. Fee: $225. Contact: UCD.

ANESTHESIOLOGY

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Fri-Sun. Contact: UCSF.

March 21-22—**Los Angeles County Society of Anesthesiologists 32nd Postgraduate Assembly.** Los Angeles Hilton Hotel. Sat-Sun. Contact: LA County Society of Anesthesiologists, 333 S Beverly Dr, Ste 111, Beverly Hills 90212. (213) 556-8865.

April 27-May 1—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Kauai Hotel, Poipu Beach, Hawaii. Mon-Fri. 20 hrs. Contact: Linda P. Londerville, CSA, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

May 1-3—**Clinical Neuromuscular Pharmacology—1987.** Anesthesiology Educational Foundation and UCLA at Palm Springs. Fri-Sun. 15 hrs. Contact: Anes Educ Found, PO Box 24230, Federal Bldg, Los Angeles 90024. (213) 825-0736.

June 25-28—**California Society of Anesthesiologists Annual Meeting.** Hotel Inter-Continental, San Diego. Thurs-Sun. 13 hrs. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

February 16-18—**Clinical Hematology and Oncology—1987.** Scripps Clinic, La Jolla at Vacation Village Resort, San Diego. Mon-Wed. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 28—**Colorectal Carcinoma—1987.** Hospital of the Good Samaritan at Moseley-Salvatori Conference Center, Los Angeles. Sat. 5 hrs. Fee: $110. Contact: Ilona Kapay-Carlos, 616 S Witmer St, Los Angeles 90017. (213) 977-2429.

March 7—**Supportive Care of the Cancer Patient.** UCI at Long Beach. Sat. 6 hrs. Contact: UCI.

March 12-14—**2nd International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. 20 hrs. Contact: UCSD.

March 18-20—**7th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. Fee: $275-325. Contact: UCSF

April 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Newporter Hotel, Newport Beach. Sun. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 1—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Vacation Village Resort, San Diego. Fri. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. Fee: $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Associate Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

CARDIOLOGY

February 18—**2nd Annual Current Concepts in the Mechanisms and Treatment of Cardiac Arrythmias.** Daniel Freeman Memorial Hospital, Inglewood. Wed. 6 hrs. Contact: Daniel Freeman Memorial Hospital, 333 N Prairie Ave, Inglewood 90301. (213) 674-7050, ext 3427.

March 22-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Royal Lahaina Hotel, Maui, Hawaii. Sun-Wed. 13 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 27-28—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 9-11—**State of the Art Cardiology: The Excitement of the 80s.** Pacific Presbyterian Medical Ctr, San Francisco. Thurs-Sat. Contact: Pacific Presbyterian Med Ctr, Continuing Education, PO Box 7999, San Francisco 94120. (415) 923-3440.

April 10-11—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Inter-Continental Hotel, San Diego. Fri-Sat. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 27-May 6—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn, Rancho Santa Fe. Mon-Wed. 40 hrs. Fee: $800. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 1-2—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in CO 798-9682.

May 24-30—**5th Annual Cardiology Update.** Institute for Medical Studies at Honolulu, Hawaii. Sun-Sat. 26 hrs. $395. Contact: Lisa Krehbiel, Inst for Med Studies, 30131 Town Ctr Dr, Ste 215, Laguna Niguel 92677. (714) 495-4499.

June 7-10—**Critical Examination Review Course.** American College of Chest Physicians at Hotel Del Coronado, Coronado. Sun-Wed. 30 hrs. Fee: $575. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (312) 698-2200.

June 10—**Cardiology: Arrhythmias.** LLU at LLU. Wed. 4 hrs. Fee: $60. Contact: LLU.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 18-20—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Waikiki Hotel, Honolulu, Hawaii. Thurs-Sat. 11 hrs. Fee: $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 25-27—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Hotel, Costa Mesa. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

July 17-18—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 31-August 1—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Harvey's Hotel, Lake Tahoe, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

(Continued on Page 174)

... reimbursement.

It should be fair.

So we wrote the book for you.

Our book contains the maximum reimbursement rates for physician services Medi-Cal pays for. What's more, all the rates are arranged using the C.M.A.'s procedure codes and descriptions.*

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*The procedure codes and procedure descriptions contained in the "Listing" are copyrighted by the California Medical Association (C.M.A.) and are used in the "Listing" with their permission. The rates and all other information are Medi-Cal's.

(Continued from Page 172)

EMERGENCY MEDICINE

February 22-27—**10th Annual UCD Winter Conference: Emergency Medicine—1987.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 27 hrs. Fee: $395. Contact: UCD.

February 28—**Major and Minor Hand Problems in the Emergency Department.** UCSF at UCSF. Sat. 7 hrs. Contact: UCSF.

March 8-13—**8th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sun-Fri. 20 hrs. Fee: $350. Contact: Medical Conferences, Inc, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. Fee: $325-440. Contact: UCSD.

April 11-18—**Infectious and Toxicologic Emergencies.** Scripps Memorial Hospital, Encinitas at Waiohai Resort and Poipu Beach Hotel, Kauai, HI. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 25-May 1—**Critical Care Medicine.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. Sat-Fri. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

May 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians—Symposium I and Advanced Emergency Procedures Laboratory.** UCSD at Hotel Inter-Continental, San Diego. Mon-Fri. 32 hrs. Fee: $325-440. Contact: UCSD.

May 13-17—**9th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

June 1-5—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 32 hrs. $420. Contact: UCSF.

June 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III and Advanced Emergency Procedures Lab.** UCSD at Hanalei Hotel, San Diego. Mon-Fri. 32 hrs. Fee: $325-440. Contact: UCSD.

INTERNAL MEDICINE

February 19-21—**Advances in the Management of Infectious Disease.** University of Michigan at Kahala Hilton Hotel, Honolulu, Hawaii. Thurs-Sat. 11.75 hrs. Fee: $285. Contact: Gayle Fox, Office of CME, Univ of Michigan, Towsley Center, Box 0201, Ann Arbor, Michigan 48109-0201. (313) 763-1400.

March 6-7—**Current Topics in Diagnosis and Therapy of Infectious Diseases.** American College of Physicians at Santa Barbara. Fri-Sat. Contact: Registration Services, ACP, 4200 Pine St, Philadelphia, PA 19104. (800) 523-1546 or (215) 243-1200.

March 7-14—**Topics in Internal Medicine for Primary Care Physicians.** University of Colorado at Molokai Sheraton, Molokai, Hawaii. One week. 20 hrs. Fee: $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

March 11—**Rheumatology: Osteoarthritis and Nonsteroidal Drugs.** LLU. Wed. 4 hrs. Fee: $60. Contact: LLU.

March 20-21—**Update in Gastroenterology—1987.** Eisenhower Medical Center, Rancho Mirage. Fri-Sat. Contact: Annenberg Ctr for Health Sciences, Eisenhower Med Ctr, 39000 Bob Hope Dr, Rancho Mirage 92270. In California, (800) 621-7322, National, (800) 321-3690.

March 30-April 1—**Federation of Western Societies of Neurological Science 24th Annual Meeting.** Mon-Wed at Hotel Del Coronado, Coronado. Contact: Patrick D. Lyden, MD, Dept of Neurosciences, UCSD Medical Center H-815A, 225 W Dickinson St, San Diego 92103. (619) 452-3940.

April 2-4—**Intrauterine Diagnosis and Treatment: The New Frontier.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. Contact: UCSD.

April 8-10—**Advances in Infectious Disease: Current Therapy.** UCSF at Hyatt Regency Embarcadero, San Francisco. Wed-Fri. 16 hrs. Fee: $350. Contact: UCSF.

April 23-24—**7th Annual Infectious Diseases—Clinical Update.** Sutter Community Hospitals and Mercy Hospital of Sacramento at Red Lion Inn, Sacramento. Thurs-Fri. 14 hrs. Contact: Infectious Diseases Symposium, Metro Centre, 1600 Sacramento Inn Way, Ste 132, Sacramento 95815. (916) 925-1366.

April 29—**Thyroid '87.** Hospital of the Good Samaritan at Moseley-Salvatori Conference Ctr, Los Angeles. Wed. 7 Hrs. Contact: Dolores Gay, Hosp of the Good Samaritan, 637 S Lucas Ave, Los Angeles 90017. (213) 977-2555.

May 2—**New Treatments in Liver and Biliary Tract Disease.** Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. Fee: $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 16—**Clinical Aspects of Viral Disease.** Grossmont District Hospital at Kona Kai Club, San Diego. Sat. Contact: Vera Belyeu, Grossmont District Hospital, 5555 Grossmont Center Dr, La Mesa 92041. (619) 465-0711, ext 245.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Mon-Fri. 32 hrs. Fee: $440. Contact: UCSF.

June 17-19—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. Fee: $375. Contact: UCSF.

June 22-26—**Advances in Internal Medicine.** UCSF at UCSF. Mon-Fri. 32 hrs. Fee: $440.

OB/GYN

February 21—**Infertility Update IV.** Scripps Clinic and Research Foundation, La Jolla. Sat. 6 hrs. Contact: Bonny Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Fri-Sun. Contact: UCSF.

March 25-28—**Gynecological Surgery With Emphasis on Vulvar and Vaginal Disease.** UCI at Hilton Riviera, Palm Springs. Wed-Sat. 16.5 hrs. Contact: UCI.

April 2-4—**Fetal Diagnosis and Treatment.** UCSD. Thurs-Sat. Contact: UCSD.

April 30-May 2—**12th Annual Symposium: Care of the Sick Newborn.** UCI. Thurs-Sat. Contact: UCI.

May 6-10—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Americana Canyon Hotel, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

June 11-13—**Gynecologic Oncology and Breast Disease.** American College of Obstetricians and Gynecologists at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave, SW, Washington, DC 20024-2588. (202) 638-5577.

June 30-July 5—**5th Annual Controversies in Obstetrics and Gynecology.** UCI at Mauna Kea Beach Resort, Hawaii. Tues-Sun. Contact: UCI.

OPHTHALMOLOGY

February 27-28—**Current Surgical Treatment for Myopia with Special Concentration in Scleral Reinforcement.** San Gabriel Valley Medical Center. Fri-Sat. 11 hrs. Fee: $275-325. Contact: Karen Frankfurt, Thompson Eye Foundation, 416 Las Tunas Dr, #102, San Gabriel 91776. (818) 289-7858.

ORTHOPAEDICS

March 11-15—**What's New and What's True in Orthopaedic Surgery.** UCD at Silverado Country Club, Napa Valley. Wed-Sun. 19 hrs. $445. Contact: UCD.

April 3-5—**Techniques of Intramedullary Nailing: Tibia, Humerus, and Femur.** Centinela Hospital Medical Center at Century Plaza Hotel, Century City. Fri-Sun. 15 hrs. Fee: $395. Contact: Jeanne Spala, DME, Centinela Hospital, 555 E Hardy St, Inglewood 90307. (213) 673-4660, ext 8213.

April 30-May 2—**American Back Society Spring Symposium on Back Pain.** Anaheim Hilton Hotel. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, 2647 E 14th St, Oakland 94601. (415) 536-9929.

May 4-8—**Osteoporosis/Spine Update.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. Contact: UCSF.

(Continued on Page 252)

Significant reduction in angina attacks...

- All-day, all-night protection
- Few CNS side effects*
- Once-a-day convenience

*The most commonly reported side effects, dizziness and fatigue, have been reported in approximately 2 of 100 patients receiving CORGARD.

CORGARD®
(nadolol tablets)

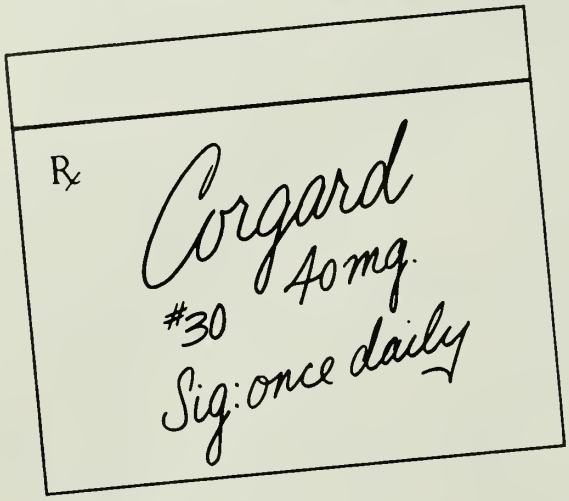
Advantages beyond control

For a complete discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, and WARNINGS, including avoidance of abrupt withdrawal, please see brief summary on adjacent page.

NOW MEDI-CAL APPROVED

CORGARD®
(nadolol tablets)

Advantages beyond control for the angina patient



CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: CORGARD (nadolol) is a synthetic non-selective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia, therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect, monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

PRINCETON PHARMACEUTICAL PRODUCTS
A SQUIBB COMPANY

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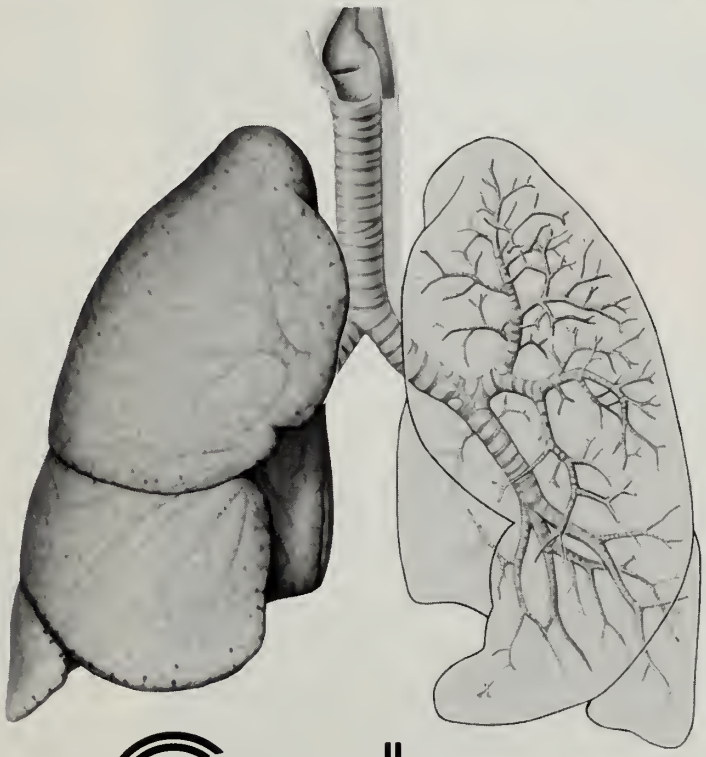
517-504 A

Issued: January 1987

Consider the causative organisms...



Ceclor®
cefaclor

250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae, H influenzae, Streptococcus pneumoniae, Streptococcus pyogenes
(ampicillin-susceptible) (ampicillin-resistant)

Note: Ceclor® is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indications: Lower respiratory infections, including pneumonia, caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci).

Contraindications: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:
- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- In renal impairment, safe dosage of Ceclor may be lower than that usually recommended. Ceclor should be administered with caution in such patients.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, erythema multiforme, serum-sickness-like reactions): 1.5%; usually subside within a few days after cessation of therapy. These reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%.

Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes.
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinitest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly)

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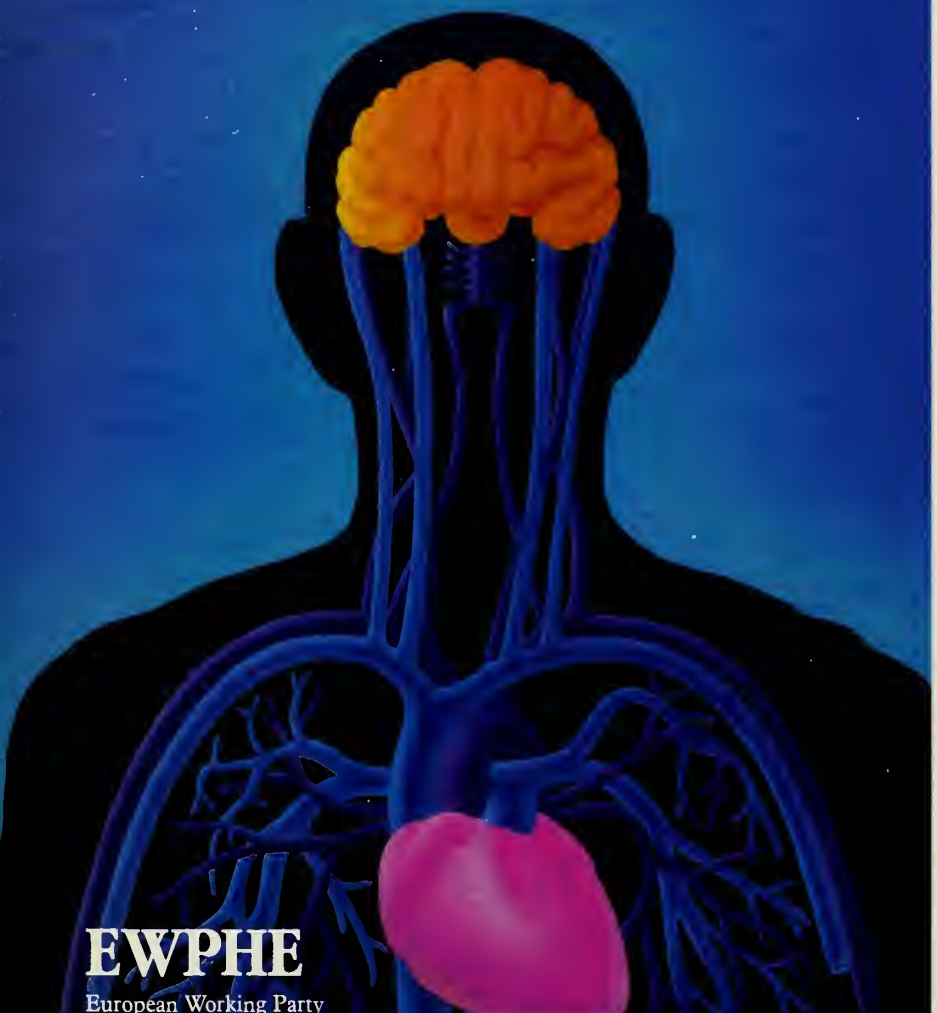
Lilly

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

600332

In Major Hypertension Trial
Most Patients Controlled on Dyazide® Alone*



EWPHE

European Working Party Trial on High Blood Pressure in the Elderly†

Confirms benefits of antihypertensive therapy

DYAZIDE®

25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

*All patients started on one 'Dyazide' per day or placebo. Dosage could be increased after two weeks to two 'Dyazide' capsules daily or two placebo capsules daily. After one month, methyldopa tablets (500 mg.) could be added. 61% of patients took only 'Dyazide' (51% one capsule and 10% two capsules). Only 35% required methyldopa.

†Amery, A., et al.: Mortality and Morbidity Results from the European Working Party on High Blood Pressure in the Elderly Trial, *Lancet* 1:1349-1354 (June 15) 1985.

Not for initial therapy. See brief summary.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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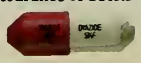

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Clinical Investigation

Abnormal Cellular and Humoral Immunity in Childhood Acute Lymphoblastic Leukemia in Long-term Remission

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The effects of multiagent chemotherapy were evaluated in 36 patients with acute lymphoblastic leukemia in long-term remission. Decreased numbers of neutrophils, lymphocytes, T cells and T-cell subpopulations (T_M, T_G, T4 [helper] and T8 [suppressor]) were found. Additional abnormalities were reduced numbers of natural killer (NK) cells, assayed using the myeloid/erythroid K562 cell line, and impaired immunoglobulin production by pokeweek mitogen (PWM)-stimulated, cultured mononuclear cells. Patients tested a year after chemotherapy was stopped showed a return to normal levels of neutrophils, lymphocytes, T, T_M and T_G cells. NK cells and the T4 cells, however, remain low, whereas the T8 cell numbers return to normal, and the helper to suppressor cell ratio remains abnormal for about three years. In experiments on PWM-stimulated cocultured cells, immunoglobulin production was decreased and abnormal T-cells, defective suppressor cell immunoregulation and relatively normal B-cell function were detected. The abnormal findings were probably the result of the multiagent chemotherapy.

(Katz J, Walter BN, Bennetts GA, et al: Abnormal cellular and humoral immunity in childhood acute lymphoblastic leukemia in long-term remission. West J Med 1987 Feb; 146:179-187)

The improved long-term survival and the possible cure of children with acute lymphoblastic leukemia (ALL) raise the question of the occurrence of long-term abnormalities in the immune system caused by intense and prolonged multiagent chemotherapy. Immunosuppression may predispose a patient to infection,[1-3] some fatal,[2] or secondary complicating malignant disorders.[4,5] Investigations of the immune system after cessation of chemotherapy have shown a decreased number of circulating leukocytes[6-8] and a rebound increase in lymphoid cells to near-normal levels three to six months later.[8] Leventhal and co-workers have reported that the chemotherapy in childhood ALL caused a mild T-cell dysfunction and a more profound depression of B cells, with some recovery after a year.[9] Others have shown that the documented decrease in immunoglobulins and antibody production increased to near-normal levels after the first year off treatment.[6,7] It does, therefore, seem that in the year following the cessation of multiagent chemotherapy, both cellular and humoral immunosuppression recover to near normal.[10] To the contrary, Layward and associates have reported prolonged T- and B-cell abnormalities even five years after stopping treatment.[11]

To further examine the long-term effects of multiagent chemotherapy in children with ALL, we evaluated patients while they were receiving multiagent chemotherapy and after stopping treatment. The numbers of leukocytes, neutrophils, lymphocytes and T cells and T-cell subpopulations T_M and T_G cells are decreased while a child is on chemotherapy and return to normal after the first year off treatment. Monoclonal antibody levels (T4 and T8) tested in treated patients were abnormal and in four patients who were retested, they returned to normal only after three years. Multiagent chemotherapy substantially depressed natural killer (NK) cell activity and pokeweed mitogen (PWM)-stimulated immunoglobulin synthesis. NK cell activity rebounded after treatment was stopped, but after six months it decreased to lower than normal levels. PWM-stimulated immunoglobulin synthesis was abnormal during the first year off treatment, and the defect appeared to be caused by a decreased number of helper cells. Allogeneic cocultures showed defective T cells and an unusual sensitivity of B cells to allogeneic normal T-cell immunosuppression.

Patients

A total of 36 patients with ALL who were younger than 14 years at diagnosis were studied: 11 were on chemotherapy and 25 were off treatment. The patients receiving chemotherapy were all in first remission for one to two years and the patients off treatment included 20 in first remission, 4 in second remission and 1 in third remission. The ages of the patients on chemotherapy were 3 to 12 years and off treatment 11 to 22 years. Evaluations were carried out in 12 patients

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Supported by grants from the Elsa U. Pardee Leukemia Foundation, Michigan, and the Cancer Research Coordinating Committee of the University of California.

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ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
FITC = fluorescein isothiocyanate
Ig = immunoglobulin
NK = natural killer (cells)
PWM = pokeweed mitogen

within the first year (mean 10 months, range 8 to 12 months) and in 13 after the first year off treatment (mean 17 months, range 15 to 21 months). PWM-stimulated immunoglobulin production was tested in five patients receiving chemotherapy, in eight less than one year off treatment and in ten more than one year off treatment, and in six of these patients the test was repeated both before and after one year. During the study period of four years, none of the patients have relapsed; in one, however, a secondary complicating acute nonlymphocytic leukemia has developed. At the time of treatment of 30 of the patients, no set protocol was followed and the patients were treated with multiagent chemotherapy for at least five years; all received standard induction therapy with vincristine sulfate and prednisone, L-asparaginase was added in four and all received the standard maintenance regimen of 6-mercaptopurine, once-a-week doses of methotrexate and monthly pulses of vincristine and prednisone.

The study included an additional six patients who had been placed on Children's Cancer Study Group protocols (the Children's Cancer Group 160 series) and received similar multiagent chemotherapy. These six patients received treatment, one for 4 years (including one relapse), one for 3½ years and four for 3 years. The laboratory tests were carried out after stopping treatment and the results were compared with those of the larger group of patients. Seven of the patients off treatment (including five patients who had relapsed) also received cyclophosphamide, and in two of the five patients who relapsed, doxorubicin (Adriamycin) hydrochloride was added to their regimen. All patients received central nervous system prophylaxis consisting of intrathecal administration of methotrexate and cranial irradiation with 2,400 rads, the patients on the Children's Cancer Study Group protocols receiving only 1,800 rads. None of the patients studied showed poor prognostic criteria at their initial presentation.

Control blood specimens were collected from adult laboratory staff aged 18 to 40 years. Informed consent was obtained from all participants and their parents in accordance with the Human Subjects Review Board at the University of California, Irvine, and Childrens Hospital of Orange County (Orange), California.

Methods

For all patients, complete blood counts were done on a Coulter counter and the absolute numbers of cells were calculated from the differential counts. The blood specimens were drawn from patients on chemotherapy at the time of the monthly intravenous pulses of chemotherapy and from patients off treatment at the time of a routine clinical evaluation.

Separation and Enumeration of T and Non-T Cells

Peripheral blood (10 to 15 ml) collected in sterile heparinized tubes was diluted 1:1 with calcium and magnesium in a free Hanks balanced salt solution, and mononuclear cells were separated on a Ficoll-Hypaque density gradient (1.074) according to the method of Böyum.[12] T cells were enumerated as E rosettes by a previously described modification[13] of the method of Wybran and colleagues.[14] T and non-T cells were purified by a modification of the method of Gupta and Good.[15] Mononuclear cells at 2×10^6 cells per ml were incubated with 1% sheep erythrocytes at 4°C overnight. An aliquot was tested for the percent of sheep erythrocyte rosetting (T cells), and the remaining cells were layered onto a Ficoll-Hypaque cushion and centrifuged at $400 \times g$ for 25 minutes. The pellet contained rosetted T cells and at the interface the non-T cells. The T-cell population was treated with water to lyse the sheep erythrocytes, and both cell populations were isolated and then washed three times with Hanks balanced salt solution. The percent of B cells was estimated by a modification of the direct fluorescent antibody technique[16] previously described[13] but using fluorescein isothiocyanate (FITC)-goat anti-human immunoglobulin $F(ab)'_2$ (Kallested, Chaska, Minn). The fluorescent B cells were enumerated under an Olympus fluorescent microscope, with at least 200 cells being counted.

T-Helper (T_M) and T-Suppressor (T_G) Cells

The percent of T_M and T_G cells was determined by incubating T cells overnight at 37°C in RPMI-1640 medium (Gibco, Grand Island, NY) supplemented with 10% fetal calf serum (Reheis, Phoenix), 2 mmol per liter glutamine, 25 mmol per liter HEPES buffer, 100 units penicillin and 100 units streptomycin per ml (all from Gibco).[15] Cells were suspended in phosphate-buffered saline solution at 7×10^6 cells per ml, and 0.1 ml of T cells was added to 0.1 ml of 2% washed ox erythrocytes coated with immunoglobulin (Ig) M or IgG from rabbit anti-ox erythrocyte serum (Cappel, Cochranville, Penn). The cell mixture was incubated at 4°C for 90 minutes. Rosetted cells were counted under the microscope, with at least 200 cells being evaluated. The absolute number of T_M and T_G cells was calculated from the absolute T-cell number.

T-Helper and T-Suppressor Cells (Monoclonal Antibodies T4 and T8) and Helper:Suppressor Cell Ratio

Ficoll-Hypaque-separated mononuclear cells were resuspended at 1×10^6 cells per ml in RPMI-1640 medium containing 2% fetal calf serum. One milliliter of cells was pelleted in a test tube at $500 \times g$ at 4°C for six minutes. The supernatant was removed and 200 μl of diluted monoclonal antibody (Coulter, Hialeah, Fla) was added to the cell pellet and vortexed gently. After 30 minutes of incubation on ice, cells were washed twice with RPMI-1640 and 2% fetal calf serum, and 200 μl of diluted goat anti-mouse immunoglobulin antibody conjugated with FITC (Kallested) was added to the cell pellet. The cells were incubated 30 minutes on ice, washed three times, resuspended in a minimal volume of RPMI-1640 and mounted on microscope slides. The number of fluorescent cells of 200 lymphocytes counted under a fluorescent Olympus microscope was recorded as a percentage.

Natural Killer Cell Assay

The target cell for the natural killer cell assay[17] was the K562 cultured cell line (obtained from Sloan-Kettering Institute, New York) grown in RPMI-1640 supplemented with 10% fetal calf serum. A total of 2×10^6 cells was washed once and incubated in 0.2 ml with 0.2 mCi sodium chromate Cr 51 (ICN, Irvine, Calif) for one to three hours at 37°C. After incubation, the cells were washed three times in 2% fetal calf serum RPMI-1640. Effector cells were mononuclear cells obtained from blood specimens of patients and normal sub-

jects. The effector cells were incubated with 1×10^4 target cells for three hours at 37°C at 100:1, 50:1, 40:1, 20:1 and 10:1 effector-to-target cell ratios. Controls for spontaneous ^{51}Cr release and total ^{51}Cr release by the addition of 5% tyloxapol (Triton X-100) were included in the assay. After incubation ^{51}Cr release was determined as counts per minute in a γ-well-counter on 0.1 ml of supernatant. The percent of lysis was calculated by dividing normal counts per minute minus spontaneous counts per minute by total counts per minute minus spontaneous counts per minute. The mean of triplicate specimens was recorded. The percent of lysis was graphed at different effector-to-target cell ratios, and lytic units (one lytic unit is that number of cells required to cause 15% specific lysis) were calculated.

Pokeweed Mitogen-Stimulated Immunoglobulin Production

The result of T-cell and non-T-cell interaction was assessed by isolating T and non-T cells as previously described and estimating immunoglobulin production in PWM-stimulated cultures.[18] Autologous non-T cells at 5×10^5 cells per ml were mixed and cocultured with T cells at the T cell-to-non-T cell ratios of 2:1, 3:1, 4:1, 6:1, 8:1 and 10:1. The cells, suspended in supplemented RPMI-1640, were incubated in Falcon flat-bottom microtiter plates (Becton Dickinson, Oxnard, Calif) in 5% carbon dioxide with or without PWM for seven days at 37°C.

Allogeneic experiments were also done wherein normal T cells were substituted for patient T cells in the same ratios. Control data were obtained by comparing similar mixed cocultures of specimens taken from normal subjects. A modified solid-phase radioimmunoassay of Catt and Tregear was carried out on the supernatants to determine IgG and IgM concentrations.[19] Polyvinyl chloride microtiter "U" plates (Dynatech, Alexandria, Va) coated with goat anti-human IgG or IgM (0.5 mg per ml; Meloy, Springfield, Va) were incubated overnight at 4°C. Plates were then washed three times with 0.05% Tween-phosphate-buffered saline washing solution. A standard curve was generated using six concentrations of human immunoglobulin (Capell) from 0.5 ng per well to 10 ng per well. Appropriate dilutions of supernatants were added in triplicate and incubated overnight at 4°C. Plates were again washed three times in washing solutions, and goat anti-human IgG or IgM (Tago, Burlingame, Calif) labeled with iodine 125 (ICN) by the chloramine-T method[20] was added and the solution incubated overnight at 4°C. Plates washed three times in washing solution and eight times in water were dried, and individual wells were counted in a Searle γ-well-counter for 60 seconds. The radioactivity counts were calculated from a standard curve and converted to immunoglobulin production in nanograms per 2×10^6 non-T cells. The amount of immunoglobulin produced (IgG and IgM) was recorded as immunoglobulin in stimulated cultures minus immunoglobulin in unstimulated cultures.

Statistical analysis of the data was accomplished by the Student's *t* test, with *P* less than .05 considered significant.

Results

Cell Counts

Significantly reduced leukocyte, polymorphonuclear neutrophil and lymphocyte counts were found only in those patients on chemotherapy. A significantly reduced number of T cells was found in patients on chemotherapy and also in those less than one year off treatment. The number of T_M and T_G cells was significantly decreased in patients receiving chemotherapy and those less than one year off treatment. B-cell numbers were normal in all patient groups (Figure 1).

Helper and Suppressor Cells (Monoclonal Antibodies T4 and T8)

The results of nine patients on chemotherapy were analyzed in Table 1. The absolute numbers of lymphocytes are recorded in addition to percentages, as patients on chemotherapy have leukopenia and lymphopenia.[2] The patients receiving chemotherapy showed significantly reduced absolute numbers of both helper and suppressor cells (*P* .003), but the percentage of helper cells was normal whereas the percentage of suppressor cells was significantly increased ($P < .02$). The mean helper-to-suppressor cell ratio was within the normal range, with ratios less than 1.0 in only two patients.

Table 2 shows the data in the ten patients who were ten months to three years off treatment. Six patients tested were more than two years off treatment. A statistically significant decreased absolute number and percentage of helper cells (T4) were found, but the number of suppressor cells (T8) was normal. The percentage of helper cells was less than 30 in eight of the ten patients and in only one of the normal subjects ($P < .001$). The ratio of helper to suppressor cells was significantly reduced ($P < .001$) and less than 1.0 in five of the ten patients, whereas in all normal subjects the ratio was greater than 1.0. More recent data on four patients more than three years off treatment showed a normal ratio of helper to suppressor cells (Table 3).

Natural Killer Cells

The number of NK cells was significantly decreased in patients on chemotherapy. During the first six months off treatment, the NK cell number showed varying levels. Three of the six patients showed a rebound to greater than normal lytic units and three had low levels. After six months, a statistically significant decrease in circulating NK lytic units per milliliter was found in the 14 patients tested (Table 4).

Pokeweed Mitogen-Stimulated Immunoglobulin Production

In autologous experiments, initially 2:1, 3:1 and 4:1 ratios were compared. IgG production was significantly reduced in the coculture ratios 2:1, 3:1 and 4:1 (T and non-T cells) in patients on chemotherapy when compared with that of controls. In patients less than one year off treatment, IgG production was significantly decreased in the coculture ratios 2:1 and 3:1, but at a 4:1 ratio IgG production increased to normal levels. In the patients off treatment for greater than a year, IgG production was significantly decreased only in the coculture ratio 2:1 (Figure 2). When compared with controls, IgM production (Figure 3) was significantly decreased in the coculture ratios 2:1, 3:1 and 4:1 in both patients on chemotherapy and those less than a year off treatment. In patients off treatment for more than a year, IgM production was significantly decreased only in the coculture ratio 2:1. Sequential comparison of PWM-stimulated immunoglobulin production in six patients off treatment for less and more than a year is shown in Table 5. After a year off treatment, IgG production increased in four patients: patient 3 showed a rise only at the 4:1 ratio, patient 5 did not show a rise in the IgG production after 15 months off treatment and patient 6 showed only a slight increase in IgG production after 18 months off treatment. Increased IgM levels were

found in all the patients tested after a year off treatment. Analysis of patients who also received cyclophosphamide is detailed in Table 6. No significant differences in PWM-stimulated IgG and IgM levels were found when compared with patients who did not receive cyclophosphamide. When significant differences were seen in the initial ratios 2:1, 3:1 and 4:1, eight patients from ten months to four years off therapy were studied at the higher T-cell to non-T-cell ratios of 6:1, 8:1 and 10:1 to determine when suppression occurred. In autologous experiments, IgG production by PWM-stimulated mononuclear cells showed an exponential rise when T-cell to non-T-cell ratios were increased from the 2:1 to 6:1 ratios (Figure 4). Suppression of the IgG production was noted when the ratios were 8:1 and 10:1. The peak levels occurred at the 6:1 ratio in the patients, whereas the IgG levels peaked at 3:1 or 4:1 ratios in the normal subjects. Suppression was noted at the 8:1 ratio in the patients and 6:1 in the normal subjects.

IgM production (Figure 5) was greatly decreased in the patient group compared with the normal control subjects. In

TABLE 1.—*Decreased Helper Cells With Normal Helper (H) and Suppressor (S) Cell Ratios in 9 Patients on Chemotherapy*

	Helper Cells (%T4)				Suppressor Cells (%T8)				H:S Ratio	
	Controls		Patients		Controls		Patients		Controls	Patients
	%	Abs No.	%	Abs No.	%	Abs No.	%	Abs No.		
	39	570	55	186	31	741	31	105	1.2	1.8
	45	1,215	35	277	21	567	17	135	2.1	2.1
	39	1,510	46	397	18	342	18	156	2.0	2.6
	29	406	35	314	21	294	42	376	1.4	0.8
	38	950	26	274	20	500	27	285	1.9	1.0
	35	665	36	140	12	228	20	18	2.9	1.8
	41	861	39	213	18	378	41	224	2.3	1.0
	34	646	19	109	19	361	25	303	1.8	0.4
	31	589	32	352	11	209	14	154	2.8	2.3
	25	475			22	418			1.1	
	31	589			23	437			1.4	
Mean	35	771	39	257	20	407	28	194	1.9	1.6
SD	6	337	9	86	5	154	11	107	0.6	0.7
*P**			.157	.001			.02	.003		.15

Abs No. = absolute numbers, SD = standard deviation

**P* values obtained by comparing percentages and absolute numbers for normal subjects versus patients ($P < .05$ considered significant).

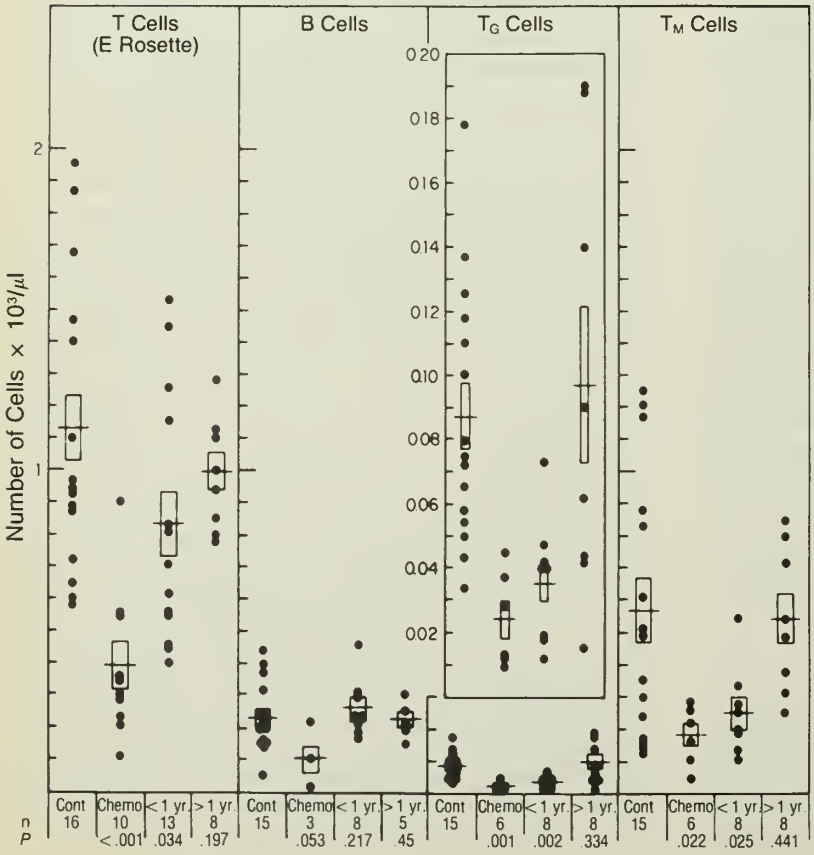

Figure 1.—Absolute number of T cells, B cells and the subpopulations of T_G and T_M cells in controls (Cont; normal subjects) and patients on chemotherapy (Chemo.) less than and greater than 1 year off treatment. A 10 × magnification of the results of the T_G cells has been inserted. Differences between the mean and standard error of the mean of controls and patient groups were evaluated by the Student's *t* test (*P* values of < .05 are considered significant).

four patients, IgM production was not suppressed even at the 10:1 ratio, and a steady rise of IgM was recorded. One patient who was 2½ years off treatment showed a plateauing of IgM levels at the 6:1 and 8:1 ratios (946 ng per 2×10^6 cells) and a

TABLE 2.—*Depressed Helper Cells and Abnormal Helper (H) to Suppressor (S) Cell Ratios in 10 Patients Off Treatment*

	Helper Cells (%T4)				Suppressor Cells (%T8)				H:S Ratio	
	Controls		Patients		Controls		Patients		Controls	Patients
	T4,%	Abs No.	T4,%	Abs No.	T8,%	Abs No.	T8,%	Abs No.		
	39	570	15	285	31	741	19	361	1.2	0.8
	45	1,215	27*	459	21	567	26	442	2.1	1.0
	39	1,510	19	361	18	342	15	285	2.0	0.8
	29	406	36	864	21	294	23	552	1.4	1.6
	38	950	18*	342	20	500	26	494	1.9	0.7
	35	665	8*	160	12	228	13	260	2.9	0.6
	41	861	19†	342	18	378	21	378	2.3	0.9
	34	646	27†	540	19	361	20	400	1.8	1.4
	31	475	26*	520	11	209	33	660	2.8	0.8
	25	589	30	510	22	418	27	459	1.1	1.1
	31	475			23	437			1.4	
Mean	35	771	23	438	20	407	22	429	2.0	1.0
SD	6	337	8	191	5	154	6	121	0.6	0.3
P Value			.003	.0066			.15	.36		.0003

Abs No.=absolute number of cells times 10^3 per μl, SD=standard deviation

*Patients off treatment for more than 2 years.
†Patients off treatment for more than 3 years.

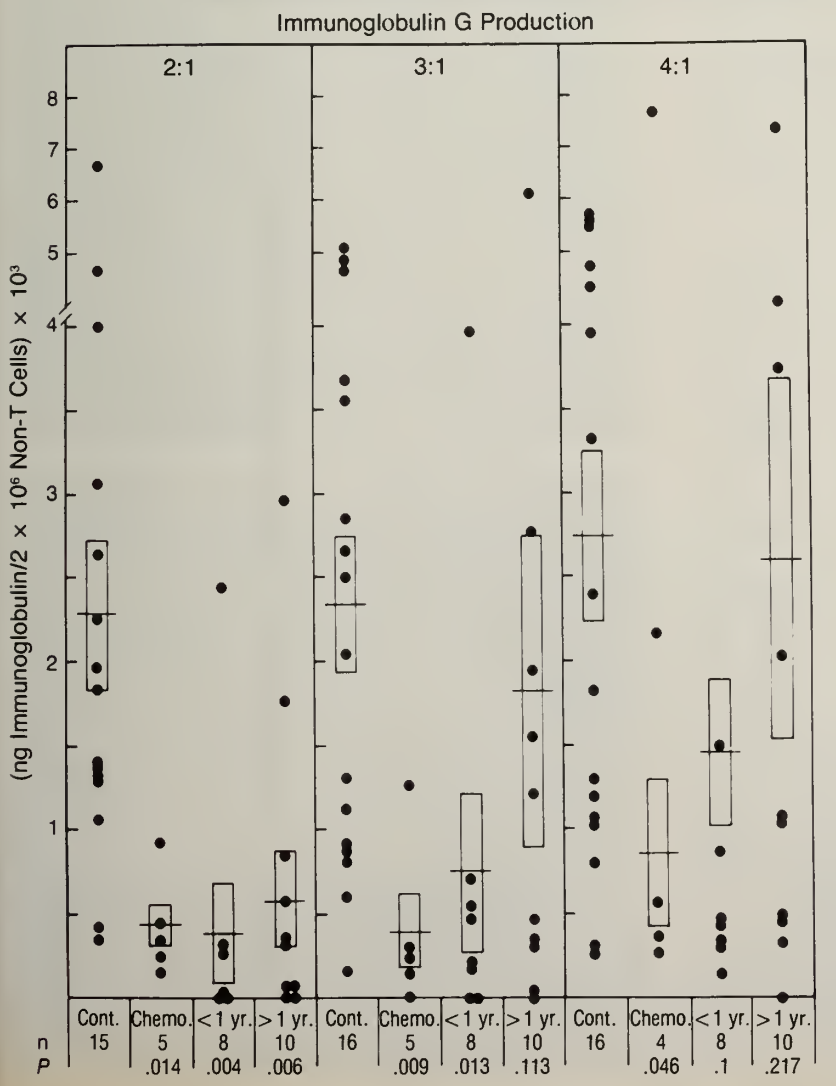

Figure 2.—The graph shows the amount of immunoglobulin (Ig) G produced in pokeweed mitogen-stimulated mononuclear cell cocultures with increasing T cell to non-T cell ratios. Differences between the mean and the standard error of the mean of the controls (Cont; normal subjects) and the patient groups on chemotherapy (Chemo.) and off treatment for less than and greater than 1 year were evaluated by the Student's *t* test (*P* values < .05 are considered significant).

slight decrease at the 10:1 ratio (547 ng per 2×10^6 cells). In three patients (3, 3½ and 4 years off treatment), plateauing of IgM occurred at the 4:1 and 6:1 ratios (mean 110 ng per 2×10^6 cells) and IgM production was suppressed at the 8:1 ratio (mean 710 ng per 2×10^6 cells). In the normal controls, IgM production was similar to IgG production and suppression was noted at the 6:1 ratio.

In allogeneic experiments, incubating normal T cells with patients' non-T cells evoked a substantial decrease of immunoglobulin production. Both IgG and IgM were affected, with suppression occurring at the 3:1 ratio, and greatly decreased at the higher ratios of 6:1, 8:1 and 10:1 (Figures 4 and 5). Control data were obtained from six experiments wherein allogeneic normal cells were cocultured in the same way. The results showed that IgG and IgM production paralleled the normal autologous cocultures.

Discussion

The highly successful treatment of childhood acute lymphoblastic leukemia has resulted in an immune deficiency, documented by many workers.[6-9,11] It is possible that this immune deficit is caused solely by multiagent chemotherapy. In this study we investigated the effects of multiagent chemotherapy on patients with leukemia and found greatly decreased total leukocyte, neutrophil and lymphocyte counts. T cells and T-cell subpopulations—T_M, T_G, T4 and T8—were also decreased. After stopping treatment, improvement to near-normal levels occurred after the first year off treatment. While receiving chemotherapy, patients have reduced numbers of helper cells (T4) and suppressor cells (T8) and normal helper-to-suppressor cell ratios, indicating that helper and suppressor cells are equally affected by chemotherapy. After stopping treatment, prolonged significantly decreased levels of T4 cells, normal T8 cell levels and abnormal helper:suppressor cell ratios were found. This indicates that the T-suppressor cells are the first to rebound and the T helpers return to normal levels at a slower rate. The abnormalities resolved in four patients three years after treatment was stopped.

Further studies showed that NK cells were decreased while a patient was receiving chemotherapy and after treatment was stopped, with the number of NK lytic units either increased or decreased during the first six months off treatment, then falling to lower than normal levels. McGeorge and co-workers previously reported that multiagent chemotherapy affected in vitro NK cell activity, but long-term effects were not found.[21] The decreased number of NK lytic

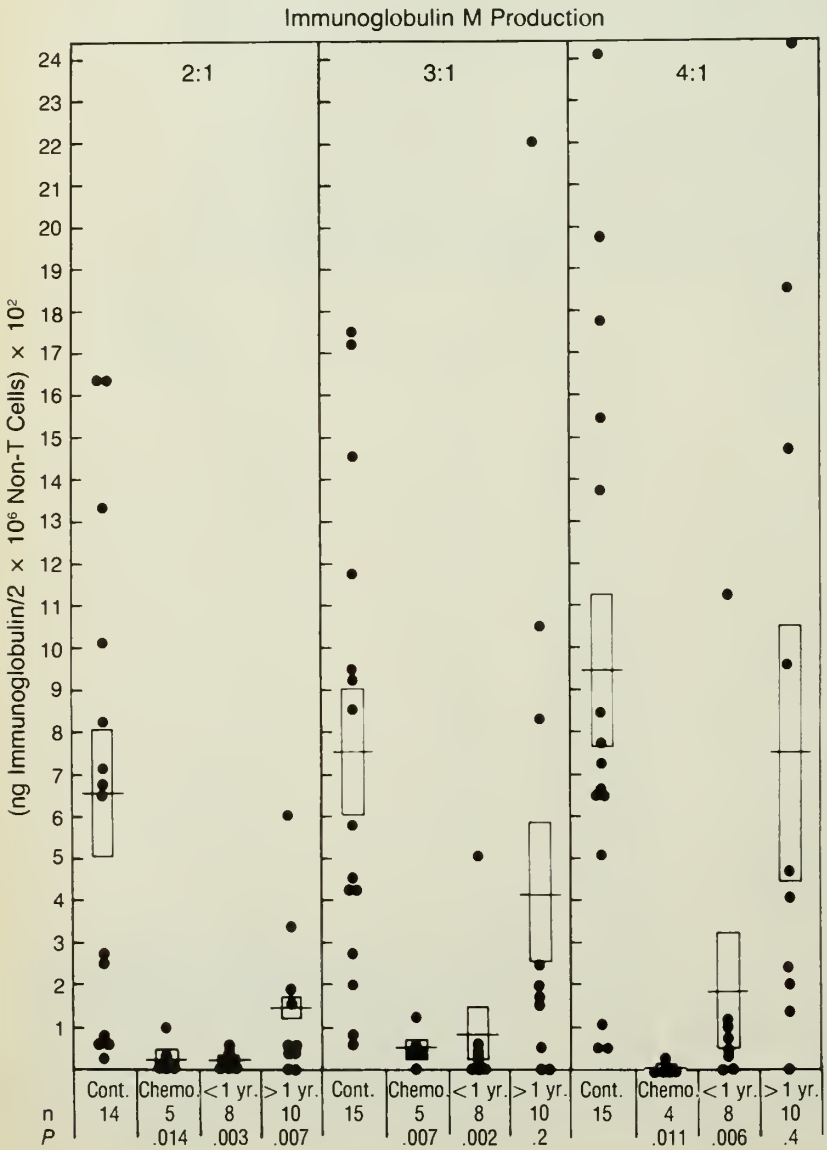

Figure 3.—The graph shows the amount of immunoglobulin (Ig) M produced in pokeweed mitogen-stimulated mononuclear cell cocultures with increasing T cell to non-T cell ratios. Differences between the mean and the standard error of the mean of the controls (Cont; normal subjects) and the patient groups on chemotherapy (Chemo.) and off treatment less than and greater than 1 year were evaluated by the Student's *t* test (*P* values < .05 are considered significant).

units detected in our study, however, may have some clinical relevance and confirms the decreased NK cell activity previously reported by Matera and Giancotti.[22]

In the normal subjects, IgM production peaked at the 4:1 ratio, whereas in four of the eight patients IgM production was grossly abnormal and normal IgM levels were detected only when 8:1 and 10:1 ratios were attained. Suppressor cell function and suppression were near normal for IgG regulation, with decreased levels at an 8:1 ratio in patients compared with a 6:1 ratio in the normal subjects. Grossly abnormal suppressor cell suppression of IgM production was found, however, and in four of eight patients IgM production was not abrogated even at 8:1 and 10:1 ratios. Decreased IgM production has been previously reported in patients with Hodgkin's disease receiving multiagent chemotherapy.[23]

In addition, our studies showed abnormal B-cell function. In cocultures of patients' B cells with allogeneic T cells, pronounced immunosuppression of both IgG and IgM production was found. This suggests that patients' B cells are abnormally sensitive to normal suppressor cell regulation. The significance of these immunologic abnormalities is not known. It is known, however, that immune disorders are associated with malignant conditions, and it can be questioned whether these patients will be prone to malignancy in later years. It has been reported that the suppressor cell system is implicated in various disease processes ranging from excessive suppressor cell activity in chronic lymphatic leukemia,[24] hypogammaglobulinemia[18] and selected IgA deficiency,[25] a suppressor cell dysfunction in systemic lupus erythematosus[26,27] and deceased activity in autoimmune disorders.[28-30] Suppressor T cells have also been shown to play a role in the immunologic enhancement of tumor growth and immune elimination of tumor cells by the host.[31] Suppressor cell dysfunction with altered immunoregulation was reported in a patient with microglobulinemia and his kindred.[32] Aberrant suppressor T cells have been reported in patients with graft-versus-host disease following bone marrow transplanta-

TABLE 3.—*Number of Helper (T4) and Suppressor (T8) Cells and T4:T8 Ratios in 4 Patients Reevaluated After 3 Years Off Treatment**

	Off Treatment 1-2 Years			After 3 Years		
	T4 Number	T8 Number	T4:T8 Ratio	T4 Number	T8 Number	T4:T8 Ratio
	27	26	1.0	45	25	1.8
	18	26	0.7	35	33	1.1
	19	21	0.9	37	21	1.8
	30	24	1.2	36	17	2.1
Mean	24	25	0.9	38	24	1.7
SD	6	3	0.2	5	7	0.4
P Value	.001	.1	.001	.1	.1	.1

SD=standard deviation

*Normal control data—see Table 1.

TABLE 4.—*Natural Killer Cell Activity in 7 Patients on Chemotherapy and 14 Off Treatment**

	Controls	On Chemo	<6 Months Off Chemo	>6 Months Off Chemo
	6.7	0.5	33.3	5.8
	17.8	1.1	45.0†	16.6†
	9.3	2.4	14.3†	8.5†
	18.0	2.0	6.4†	7.8†
	23.3	0.7	4.2	4.5
	37.1	1.0	2.0	8.5
	11.4	2.5		10.4
	5.3			9.6
Mean	16.2	1.5	17.5	9.0
SD	10.1	0.8	17.6	3.6
n	8	7	6	8
P Value		.001	.4262	.045

Chemo=chemotherapy, SD=standard deviation

*In circulating lytic units per milliliter blood. 1 lytic unit=15% lysis
†Patients reevaluated before and after 6 months.

TABLE 5.—*Sequential Comparison of Pokeweed Mitogen-Stimulated Immunoglobulin Production in 6 Patients Less Than 1 Year and Greater Than 1 Year Off Treatment*

		Immunoglobulin (Ig) Production			
		IgG		IgM	
Patients	Ratio of T Cells to Non-T Cells	<1 Year	>1 Year	<1 Year	>1 Year
1	3/1	197	6,175	34	1,050
2	...	184	1,563	12	176
3	...	478	186	0	65
4	...	561	1,210	40	235
5*	...	704	308	64	200
6	...	0	480	0	10
1	4/1	825	7,375	124	1,866
2	...	353	2,048	53	144
3	...	456	715	0	322
4	...	350	1,068	112	475
5*	...	427	361	80	240
6	...	200	494	0	961

*Patient 5 showed no rise in IgG levels.

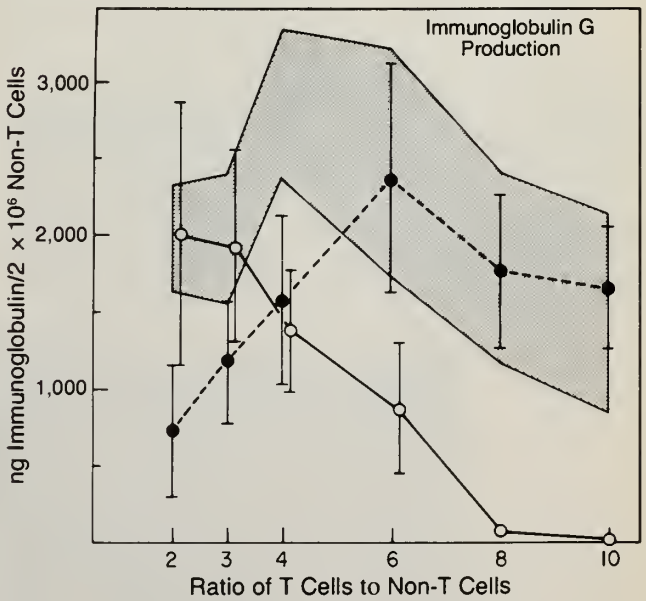

Figure 4.—The suppressor cell effect on immunoglobulin (Ig) G production in pokeweed mitogen-stimulated cultures is compared in patients and normal controls. The hatched area represents the range of 18 normal experiments (10 autologous and 8 allogeneic) showing peaking of IgG at 4:1 and suppression starting at 6:1 ratios (T cells to non-T cells). ●---● represents the mean and standard error of the mean (SEM) of IgG production of the 8 patients tested with peaking of IgG production at 6:1 and immunosuppression at 8:1 and 10:1 ratios; ○---○ represents the mean and SEM of IgG production in 8 patients where allogeneic normal T cells were substituted for patients' T cells.

tion,[33,34] and this state is associated with a higher than normal incidence of malignant disorders. The impaired suppressor cell activity, mild for IgG suppression and more substantial for IgM immunosuppression, may be accounted for by postulating that a critical level of immunoglobulin production is required for suppressor cell function to be "turned on" or helper activity to be "switched off." It is also evident that suppressor cell activity is present, but there is a delay in the reactivation of IgM suppression. The preliminary findings require further confirmation and investigation. In the follow-up of these patients over the three-year period of the present study, none of these patients has relapsed. In one of the 19 patients, however, a secondary complicating leukemia recently developed, which may mean that when an immune-compromised state reverts to normal, a susceptibility to the development of secondary (complicating) malignant tumors may result. Further long-term follow-up is required to determine the significance of the abnormal chemotherapy-induced cellular and humoral immunity in a patient with childhood leukemia in long-term remission. To date, the patients as a group have done well. There have not been major infections developing after chemotherapy was stopped. This may have been expected given the increased percentage of suppressor cells, a decreased number of helper cells and a decreased number of natural killer cells. It appears that the impaired immune state did not significantly increase the severity or frequency of infections the year after chemotherapy was stopped.

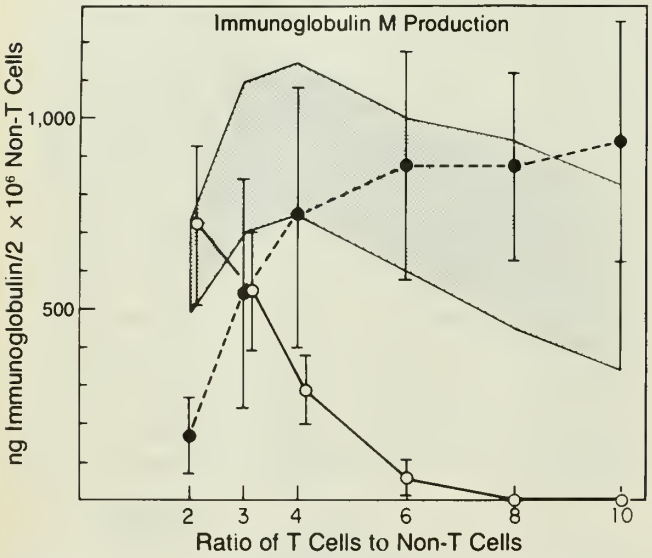

Figure 5.—The suppressor cell effect on immunoglobulin (Ig) M production in pokeweed mitogen-stimulated cultures is compared in patients and normal controls. The hatched area represents the range of 18 normal experiments (10 autologous and 8 allogeneic) showing peaking of IgM at 4:1 and suppression starting at 6:1 ratios (T cells to non-T cells). ●---● represents the mean and standard error of the mean (SEM) of IgM production of the 8 patients tested, with continued increase of IgM production at the 10:1 ratio; ○---○ represents the mean and SEM of IgM production of 6 patients where allogeneic normal T cells were substituted for patients' T cells.

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TABLE 6.—*Comparison of Pokeweed Mitogen (PWM)-Stimulated Immunoglobulin Production in 9 Patients Receiving Multiagent Chemotherapy With and Without Cyclophosphamide**†

	PWM-Stimulated Immunoglobulin Production‡							
	Cyclophosphamide, T Cells: Non-T Cells				*No Cyclophosphamide, T Cells: Non-T Cells*			
	3:1		*4:1*		*3:1*		*4:1*	
	IgG	*IgM*	*IgG*	*IgM*	*IgG*	*IgM*	*IgG*	*IgM*
	6,175	1,056	7,375	1,866	1,961	837	3,749	1,473
	186	65	715	322	1,563	176	2,048	144
	2,787	2,280	4,147	2,813	320	160	512	208
	308	200	361	240	1,210	253	1,068	475
	480	0	494	961				
Mean	1,987	720	2,618	1,240	1,264	357	1,844	576
SEM	1,152	434	1,382	489	350	162	710	308

SEM=standard error of the mean

*Patients more than 1 year off treatment, 5 received cyclophosphamide.
†*P* values not significant (>.05).
‡The values represent absolute numbers, as described in text.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Vertebral Artery Surgery

QUESTIONS:

Under what conditions and for which diagnoses or symptoms is vertebral artery surgery indicated?

If the surgery is allowable, what diagnostic testing is indicated prior to surgery?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery and Neurosurgery, the indications for vertebral artery surgery are relatively infrequent in the treatment of cerebrovascular disease. However, where vertebrobasilar insufficiency is clearly related to neurological signs and symptoms and is caused by a demonstrable intraluminal or extraluminal process, vertebral artery surgery is appropriate. Such conditions may include vascular occlusive disease, when one artery is occluded and the other is stenotic; aneurysms, resulting from trauma, arteriosclerosis or mycosis; vascular malformations, and elective occlusion or embolization in the treatment of vascular lesions of the posterior fossa. The type of surgical repair depends upon local anatomical and pathological factors.

The symptoms of vertebrobasilar insufficiency include but are not limited to vertigo, speech defects, bilateral visual defects, ataxia, transient hemiparesis (unilateral, bilateral or alternating), syncope and drop attacks. Often transient deficits of other cranial nerves are also present. Usually more than one symptom is present, and vertigo or dizziness alone should not be considered evidence of vertebrobasilar insufficiency.

Before surgery, a patient should have a thorough neurological examination and angiography of extracranial and intracranial circulation. Complete arch aortography and four-vessel angiography in multiple planes with serial views remain the diagnostic procedures of choice. Magnetic resonance imaging and digital subtraction angiography may also be helpful in some cases.

Postdefibrillation Idioventricular Rhythm—A Salvageable Condition

JEROME R. HOFFMAN, MD, *and* LYNNE WARNER STEVENSON, MD, *Los Angeles*

While patients who present with a pulseless idioventricular rhythm have a dismal prognosis, such a rhythm following electrical defibrillation from ventricular fibrillation (VF) may have an entirely different clinical significance. By reviewing the cases of 100 consecutive patients with prehospital ventricular fibrillation, we found the following: Subsequent development of field pulses, survival to hospital admission and hospital discharge in 49 patients who initially had pulseless idioventricular rhythm following defibrillation were statistically significantly worse (P< .05) than for 20 patients successfully defibrillated into any other organized rhythm. They were statistically significantly better, however, than for 25 patients who failed to achieve any organized rhythm in the field. Outcomes were statistically no different in 40 patients who received standard advanced cardiac life support drug therapy for pulseless idioventricular rhythm after defibrillation than in 9 patients who spontaneously progressed to another rhythm before drug therapy could be given. These findings suggest that pulseless idioventricular rhythm may be a transient recovery rhythm following defibrillation from prehospital VF, that it can in this circumstance be associated with a good outcome in a reasonable number of patients and that a short trial of cardiopulmonary resuscitation only, without immediate drug therapy, may be appropriate in these patients.

(Hoffman JR, Stevenson LW: Postdefibrillation idioventricular rhythm—A salvageable condition. West J Med 1987 Feb; 146:188-191)

Idioventricular rhythm is generally considered an almost uniformly nonviable rhythm in patients with cardiac arrest. While it is true that almost all survivors of cardiac arrest present with ventricular tachycardia or ventricular fibrillation (VF) and that patients presenting with any other rhythm, including idioventricular rhythm, asystole, severe bradycardia or electromechanical dissociation (EMD), have a dismal prognosis,[1-3] the development of one or more of these rhythms following defibrillation from VF may have an entirely different significance. We reviewed all recorded tapes and typed manuscripts of these tapes for patients with prehospital VF treated by paramedics under the direction of the UCLA base station during a 19-month period to determine the prognostic significance of rhythms seen subsequent to successful defibrillation from VF. We evaluated as well the relationship between outcome and specific mode of therapy for postdefibrillation idioventricular rhythm. We postulated that the development of an idioventricular rhythm immediately following defibrillation represents a transient recovery rhythm that can in some cases spontaneously improve, leading to the appearance of pulses, supraventricular activity, stabilization of hemodynamic status and possible long-term survival.

Materials and Methods

UCLA Medical Center is a 750-bed acute care hospital that serves as a paramedic base hospital in the west Los Angeles region. Paramedic radio calls are supervised at the UCLA base station by a physician or mobile intensive care nurse (MICN). Base station physicians are UCLA residents or faculty who have successfully completed the advanced cardiac life support course of the American Heart Association and the base station physician's course of the American College of Emergency Physicians. MICNs are registered nurses specially trained and certified to answer paramedic radio calls. Base station contact is mandatory for all cases of cardiac arrest. Cardiac patients receive prehospital care and are then transported to one of seven receiving hospitals. Continuous tape recordings are made of all radio communications, and written records, including electrocardiographic monitor strips when appropriate, are kept for all cases. During the time of this study, paramedics were authorized to secure an airway with an esophageal obturator airway and to defibrillate before establishing base station radio contact. They could carry out base station orders to place an intravenous catheter and to administer standard drugs, including but not limited to epinephrine, atropine, isoproterenol hydrochloride, calcium chloride, sodium bicarbonate, lidocaine and bretylium tosylate.

We reviewed 104 consecutive paramedic radio calls to the UCLA base station from January 1980 to August 1981 in which patients with prehospital cardiac arrest had an initial rhythm of ventricular fibrillation. Four patients with VF following drowning, electrocution or traumatic injury were ex-

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ABBREVIATIONS USED IN TEXT

EMD = electromechanical dissociation
MICN = mobile intensive care nurse
VF = ventricular fibrillation

cluded. Six patients were excluded because their subsequent arrival at an emergency department could not be documented. This left 94 study patients, for all of whom data were collected by reviewing all tape recordings in their entirety and all written records for each case. An idioventricular rhythm response to defibrillation, the development of subsequent cardiac rhythms and the presence or absence of pulses in the prehospital setting were documented. Precise data were frequently not available regarding the time of unresponsiveness, although tapes and rhythm report forms were carefully reviewed in an attempt to ascertain certain information. The usual response time of paramedic units was from three to ten minutes, but specific times were poorly documented. Patient rhythms were successfully telemetered in about a third of cases, and rhythms were otherwise interpreted by the paramedics at the scene. For the purposes of this article, we defined an organized cardiac rhythm as any electrical activity other than ventricular fibrillation or asystole. Idioventricular rhythm was defined as an organized cardiac rhythm with wide complexes appearing at a rate of less than 60 times per minute, without visible P waves. When such wide complexes occurred sporadically at a rate of less than ten times per minute, the rhythm was considered agonal and described as asystole. Wide QRS-complex rhythms at a rate greater than 100 times per minute were considered to represent ventricular tachycardia, whereas wide QRS-complex rhythms occurring at a rate between 60 and 100 times per minute were classified as "other ventricular rhythms." Palpable pulses were considered present when the paramedics were able to palpate carotid or femoral pulses, which they endeavored to do following any attempt at defibrillation, immediately following any change in cardiac rhythm and every two to four minutes during an organized cardiac rhythm.

Prehospital therapy for ventricular fibrillation was based on standard protocols, although variations in therapy were ordered at the discretion of the base station physician or MICN. In most cases of cardiac arrest with a presenting rhythm of VF, paramedics initiated therapy with countershock at 400 watt seconds of stored energy, which was the amount of energy recommended in the standard American Heart Association protocol at the time of the study. In several cases, however, sodium bicarbonate or epinephrine (or both) was administered intravenously through a catheter before the first countershock. When field stabilization—defined as the establishment of a consistent palpable pulse—was achieved, patients were transported to the closest of seven receiving hospitals. Patients who remained pulseless or who became pulseless again following the development of a transient palpable pulse were treated according to standard algorithms and were transported at the discretion of the base station or MICN only when a trial of drug therapy produced no apparent effect. Admissions to hospitals were identified from emergency department records. Discharge from hospital alive or in-hospital death was determined from patient hospital records.

We defined outcomes in terms of the development of pulses and hospital admission, as well as survival to hospital discharge. While hospital discharge is clearly the most important "successful" outcome, we also looked at the other two intermediate outcomes and considered them at least partially "successful" responses to therapy, as they may predict increased likelihood of survival to hospital discharge if subsequent interventions are optimal.

Statistical comparisons of noncontinuous data were made by Fisher's exact test; we considered a P value of less than .05 as statistically significant.

Results

Of 94 patients included in the series, 69 had the development of organized rhythm at some point during the prehospital phase, while 25 did not. Outcome was dismal for patients in whom an organized rhythm did not develop (no patient discharged alive), as it was for patients in whom an organized rhythm, but not a pulse, developed in the field (no one discharged alive). Of the 69 patients who ultimately had an organized rhythm develop, survival was significantly better in the 57 patients responding to the first two countershocks (16%) than in those 12 patients in whom a rhythm developed only after multiple countershocks (one long-term survivor).[4]

The initial heart rate associated with the first organized rhythm was documented in 69 patients (Table 1). Patients with bradycardia had significantly poorer survival to hospital admission and discharge than patients whose initial heart rate equaled or exceeded 60 beats per minute; nevertheless, 27 (50%) of the patients with bradycardia achieved pulses in the field, 15 (28%) were admitted to hospital and 5 (9%) survived. These numbers are comparable to those for the initial cohort of 94 patients with VF as a whole, of whom 40% (38 patients) achieved pulses in the field, 26% (24) were admitted and 11% (10) were discharged alive.

Of the 69 patients in whom an organized rhythm developed, a good outcome could be achieved regardless of the specific nature of that initial rhythm (Table 2). While outcome was statistically worse when the initial postdefibrillation rhythm was idioventricular (49 patients) than with other rhythms, a pulse developed at one point during the resuscitation of 47% of patients with this rhythm, 27% were admitted to the hospital alive and 8% were discharged from the hospital alive. These numbers were not statistically different from those of the original cohort with VF and are far better than the results for patients failing to have any organized rhythm in the field (Table 2).

The large majority of patients in whom idioventricular rhythm developed were initially pulseless at the time this rhythm occurred; only 3 patients with such a rhythm following defibrillation had a pulse at the time this rhythm appeared, whereas 46 patients had an initially pulseless rhythm.

TABLE 1.—*Outcome Related to Initial Postdefibrillation Heart Rate in 69 Patients With an Organized Rhythm**

		Outcome		
Heart Rate, Beats/min	*Patients, No.*	*Eventual Pulses in the Field, No. (%)*	*Admitted, No. (%)*	*Discharged Alive, No. (%)*
<60 . . .	54	27(50)	15(28)	5(9)
≥60 . . .	15	11(73)	8(53)	5(33)
Totals . . .	69	38(55)	23(33)	10(14)
P		NS	<.01	<.01

NS = no significance

*An organized rhythm is any rhythm other than ventricular fibrillation or asystole.

While none of the 3 patients with pulses accompanying their initial idioventricular rhythm were either admitted to hospital or survived to discharge, 18 patients with such a rhythm who initially were pulseless subsequently had a pulse during the prehospital resuscitation, 15 were admitted to hospital alive and 4 were discharged alive. Of these patients, 13 first had the development of pulses at a time when they remained in an idioventricular rhythm.

Subsequent rhythm evolution and drug therapy during idioventricular rhythm were evaluated in the 49 patients who had such a rhythm immediately following defibrillation (Tables 3 and 4). Patients with persistent idioventricular rhythm throughout their prehospital course were not statistically different from the entire group, while 19 patients with this rhythm degenerating to recurrent VF less frequently achieved pulses or hospital admission and showed a trend toward a poorer outcome with regard to hospital discharge, although this latter difference did not reach statistical significance because of the small numbers involved (Table 3).

We do not have information regarding the timing of subsequent therapy for patients in whom postdefibrillation idioventricular rhythm developed, and thus we cannot say how long therapy was withheld following the development of the rhythm. We do have information, however, as to what types of therapy were given to patients with this rhythm before any other rhythm developed (Table 4). In the small number of patients (nine) who received no therapy, the idioventricular rhythm either spontaneously reverted to VF (3 patients, in whom there was no survival) or spontaneously converted to a perfusing rhythm (six patients) with palpable pulses; five of these latter patients were admitted, with one surviving to hospital discharge.

There was a trend toward worse outcome by all measurements for the much larger number of patients who received drug therapy; this reached statistical significance ($P < .05$) only with regard to hospital admission. In addition, a similar but slightly greater proportion of patients receiving drugs had recurrent VF during their resuscitation. No patient with recurrent VF at any time in the field survived to hospital discharge.

TABLE 2.—*Outcome in Patients With Postdefibrillation Idioventricular Rhythm (IVR) Compared With Patients With Other Initial Organized Rhythms and Patients Without Any Organized Rhythm in the Field*

Initial Postdefibrillation Rhythm in Field	Patients, No.	Outcome: Eventual Pulses, No. (%)	Outcome: Admitted, No. (%)	Outcome: Discharged, No. (%)
IVR	49	23(47)	13(27)	4(8)
Supraventricular bradycardia	5	4(80)	2(40)	1(20)
Other supraventricular	12	8(67)	6(50)	4(33)
Unknown	3	3(100)	2(67)	1(33)
No organized rhythm	25	0(0)	1(4)	0(0)
Totals	94	38(40)	24(26)	10(11)
*P**		<.05	NS	<.025
P†		<.001	<.025	NS

NS = no significance

*Comparing IVR to all other organized rhythms.
†Comparing IVR to absence of any organized rhythm.

TABLE 3.—*Outcome Related to Subsequent Rhythm Evolution in the Field in 49 Patients With an Idioventricular Rhythm (IVR) After Defibrillation*

Rhythm	Patients, No.	Pulses, No. (%)	Admitted, No. (%)	Discharged, No. (%)
Persistent IVR	20	11(55)	7(35)	2(10)
Recurrent VF	19	5*(26)	2(11)	0(0)
Asystole	4	2†(50)	0(0)	0(0)
Supraventricular rhythm	6	5(83)	4(67)	2(33)
Total	49	23(47)	13(27)	4(8)
P‡		NS	NS	NS
P§		<.025	<.05	NS

NS = no significance, VF = ventricular fibrillation

*Includes 1 patient with pulses at the time of development of IVR.
†Includes 2 patients with pulses at the time of development of IVR.
‡Comparing persistent IVR with all others.
§Comparing recurrent VF with all others.

Discussion

The rhythms of cardiac arrest include ventricular tachyarrhythmias (ventricular tachycardia or fibrillation), bradyasystolic rhythms and electromechanical dissociation. Idioventricular rhythm is generally included with bradyasystole and EMD as a rhythm associated with a uniformly dismal prognosis. It has been our experience, however, that while only a few patients with cardiac arrest present with idioventricular rhythm, in many patients such a rhythm will develop immediately following defibrillation from VF.[4] In this circumstance, in contradistinction to idioventricular rhythm as the initial rhythm of arrest, a satisfactory outcome may be achieved, even in patients in whom such a rhythm is initially unassociated with a palpable pulse. In many of these patients a pulse subsequently develops, either while remaining in idioventricular rhythm or at the time of conversion to another rhythm. While patients having other postdefibrillation organized rhythms have an even better rate of survival, the development of idioventricular rhythm following defibrillation leaves a patient with a prognosis that is neither better nor worse than it was before defibrillation and statistically better than the prognosis for patients in whom defibrillation fails to produce any organized rhythm.

The same can be said with regard to the heart rate associated with the initial postdefibrillation rhythm: a heart rate of 60 per minute or more is clearly preferable to bradycardia; the latter, however, does not by any means preclude survival. The outcome for patients with postdefibrillation bradycardia is remarkably similar to that for all patients with VF before defibrillation and much better than that for patients failing to achieve an organized rhythm.

TABLE 4.—*Outcome Related to Prehospital Drug Therapy Given to 49 Patients With Postdefibrillation Idioventricular Rhythm Before Development of Any Other Rhythm*

Drug Therapy	Patients, No.	Recurrent VF, No. (%)	Pulses, No. (%)	Admitted, No. (%)	Discharged, No. (%)
None	9	3(33)	6(67)	5(56)	1(11)
Atropine*	29	12(41)	11(38)	8(28)	2(7)
Epinephrine*	10	4(40)	2(20)	2(20)	1(10)
Isoproterenol*	7	2(29)	2(29)	1(14)	1(14)
Calcium*	14	9(64)	6(43)	2(14)	1(7)
Totals	49†	19(39)	23(47)	13(27)	4(8)

VF = ventricular fibrillation

*Includes patients given each individual drug alone or in combination with other listed agents.
†Patients receiving various drug combinations were only counted once.

Thus, the results of early defibrillation strongly predict the outcome. Defibrillation into an organized rhythm other than an idioventricular rhythm, with a heart rate of 60 or higher, significantly improves prognosis. Defibrillation into an idioventricular rhythm or another bradycardia neither improves nor worsens predicted outcome compared with the initial VF cohort as a whole. Failure to successfully defibrillate a patient into an organized rhythm early in the resuscitation is catastrophic, leaving minimal chance for a good outcome.[4,5]

Because survival is distinctly possible following the development of postdefibrillation idioventricular rhythm, the therapeutic approach to such patients is critical. No patients in whom recurrent VF developed in our series survived to hospital discharge; any therapy given patients with a postdefibrillation idioventricular rhythm that is potentially arrhythmogenic should be considered possibly deleterious in light of this fact.

In our series patients were not treated according to a strict protocol, but we suspect that all patients with a pulseless idioventricular rhythm had prompt orders for drug therapy. We therefore suspect that the nine patients who did not receive drug therapy before another rhythm developed fell into this category only because their condition spontaneously improved or deteriorated too rapidly for drug therapy to be administered. A third of these patients degenerated into recurrent VF, whereas in the others pulses developed with or without a simultaneous change in rhythm and heart rate.

We have no idea how many patients with pulseless idioventricular rhythm following defibrillation might similarly have changed their rhythm and hemodynamic status if drug therapy had been deliberately delayed. The alternative of immediate aggressive drug therapy is not particularly attractive. Drug therapy with any or all of the standard agents recommended for the treatment of this rhythm was associated in our series with a high incidence of recurrent VF and a generally low rate of survival to hospital admission and discharge. None of these drugs are particularly benign in patients with significant heart disease. Atropine,[6-8] isoproterenol,[9] epinephrine[10] and calcium chloride[11] all dramatically increase myocardial oxygen demand and are notably arrhythmogenic. None has been independently proved to improve survival in humans with cardiac arrest from VF.[11-15]

Considering the fact that an idioventricular rhythm following defibrillation appears to be a salvageable rhythm and considering the fact that standard drugs used to treat patients with such a rhythm are potentially dangerous and seem associated with a high incidence of recurrent VF, which in our hands has been uniformly associated with fatality, we suggest that drug therapy be withheld for at least 30 to 60 seconds following development of the rhythm after defibrillation.

We recognize that this may also be associated with a high incidence of recurrent VF, although our numbers are too small to make any definitive statement. Ultimately, however, watchful waiting for a short period of time seems most likely to be safe and potentially beneficial in this situation. The prognosis remains relatively reasonable following the development of postdefibrillation idioventricular rhythm, whereas the development of recurrent VF is disastrous. Thus, avoiding the use of potentially cardiotoxic agents as long as there is a reasonable chance that they are unnecessary seems prudent.

We do not presume to know how often such a delay would lead to spontaneous improvement or how often it would result in either no change or deterioration. Using only cardiopulmonary resuscitation for 30 or 60 seconds, without drugs, would be unlikely to matter in patients who remained in idioventricular rhythm. Recurrence of VF would, of course, be deleterious, although the ability of prior standard drug therapy to prevent this in such patients is also a matter for speculation only. The possibility that antiarrhythmic therapy (lidocaine or bretylium) at the onset of postdefibrillation idioventricular rhythm might be beneficial is intriguing, considering the fact that this rhythm is generally thought to contraindicate using such agents[16]; for this reason, we would be hesitant to recommend them until larger groups of patients were evaluated.

We suspect that this extremely common postdefibrillation rhythm represents a transient stage of myocardial recovery in many patients, related to temporary suppression by the defibrillating shock of either supraventricular pacemaker activity or atrioventricular nodal conduction. We suspect that a good number of patients with idioventricular rhythm following defibrillation might spontaneously progress to a more stable rhythm and palpable pulses if treated with only external cardiopulmonary resuscitation as necessary and no drug intervention for a period of 30 to 60 seconds, and that this might reduce the risk of the development of recurrent VF associated with the use of standard drug therapy. We are currently embarked on a prospective trial to evaluate such an approach.

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Cheyletiella blakei, an Ectoparasite of Cats, as Cause of Cryptic Arthropod Infestations Affecting Humans

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Cheyletiella blakei, *an ectoparasitic mite of domestic cats, can cause an extremely annoying, persistent and pruritic dermatosis of obscure origin (cryptic infestation) in susceptible persons having close contact with infested cats. Although the prevalence of cheyletiellosis in humans and cats appears to be low, evidence of its occurrence in California is increasing. Cheyletiellosis is often underdiagnosed in both its natural host and in humans. The small size of the mite, lack of publicity about the disease, frequent absence of symptoms in infested cats and failure to recover the mite from humans contribute to its delayed recognition. When* C blakei *or other mites are suspected of being the cause of a dermatosis, medical entomologists may help to hasten the diagnosis by examining the patient's physical surroundings, potential vertebrate hosts and other sources for the presence of mites. After* C blakei *has been eliminated from cats with an appropriate pesticide, the disease in humans is self-limiting.*

(Keh B, Lane RS, Shachter SP: *Cheyletiella blakei,* an ectoparasite of cats, as cause of cryptic arthropod infestations affecting humans. West J Med 1987 Feb; 146:192-194)

Several mites including *Cheyletiella blakei,** a widely distributed ectoparasite of domestic cats, are capable of causing cryptic infestations in humans.[1-3] This mite and the related *Cheyletiella yasguri* on dogs produce a skin condition referred to as cheyletiellosis. We refer to such infestations on humans caused by either species as human cheyletiellosis, on cats caused by *C blakei* as feline cheyletiellosis and on dogs caused by *C yasguri* as canine cheyletiellosis.

Typically, members of a household in which one or more infested cats live report persistent pruritic lesions (see below) but are unaware of their cause until *C blakei* is found weeks or months later. After this mite is eliminated from a cat, members of the household recover quickly without treatment—that is, the disease is self-limiting.[4-8]

Recovery of *C blakei* from cats (or *C yasguri* from dogs) is essential for establishing a diagnosis of human cheyletiellosis. To our knowledge there has been no published account in which a diagnosis of this disease was made on the basis of clinical evidence alone. Moreover, when a patient is unable to provide a clue as to the probable cause of the pruritus, and when veterinarians do not detect the mite on a cat, the complaint goes undiagnosed.

Among factors that tend to obscure the cause of feline cheyletiellosis is the small size of the mite, which ranges to as much as 500 microns in body length. Thus, the mites are scarcely visible to the naked eye and are easily overlooked.[8,9] Further, very few lay persons or medical practitioners seem to be aware of its existence. The frequent lack of obvious symptoms in the natural host, the domestic cat, also contributes to the failure of patients to recognize the specific cause of their dermatitis. In our experience and that of others, dermatoses caused by *Cheyletiella* mites are commonly underdiagnosed in patients.[4,10]

The first published account of the occurrence of *C blakei* in California appeared in 1975.[6] In that infestation, a mother and her 5-year-old daughter were afflicted with the disease in Berkeley, Alameda County, in July 1974. Since then three additional infestations involving one to five persons have come to our attention. These include cases in Palo Cedro, Shasta County (April 1979), Petaluma, Sonoma County (August 1979), and Berkeley (March 1985). The Shasta and Sonoma County records are from the files of the California State Department of Health Services and were made available to us through the courtesy of Mr Gail Grodhaus.

The purpose of this communication is to alert the medical community to increasing evidence of *C blakei* occurrence in California, to present detailed case history information about the latest outbreak, to summarize some of the difficulties inherent in diagnosing human and feline cheyletielloses and to call attention to methods used by medical entomologists in investigating cryptic arthropod infestations.

Report of an Outbreak

The patient, aged 44 years, her husband and a daughter live in Berkeley, California. They purchased a 4-month-old white female Persian cat from a dealer in San Francisco in mid-December 1984. About four weeks later the mother began having pruritus that occurred daily during the late afternoon. In early February she traveled out of the country and

**Cheyletiella parasitivorax* was originally the name applied to *Cheyletiella* mites found on rabbits, cats and dogs. Smiley (Proc Entomol Soc Wash 1965; 67:75-79) recognized *Cheyletiella* on cats as a distinct species and later likewise (Ann Entomol Soc Am 1970; 63:1056-1078) recognized *Cheyletiella* on dogs as distinct. *C parasitivorax* remains one of two *Cheyletiella* species occurring on rabbits.

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her symptoms ceased but resumed on her return three weeks later.

Affected parts of her body included the breasts and anterior trunk down to the waist, the back and occasionally the arms and legs. The lesions were urticarial papules that typically occurred in clusters of three or four. According to the patient, they were first observed soon after the onset of pruritus and resembled mosquito bites. Rapid swelling and irritation occurred in some affected areas, though other areas did not react until the following day. She had difficulty breathing and experienced emotional distress. The lesions disappeared slowly over a period of weeks.

Her 7-year-old daughter was similarly, albeit less severely, affected. Her husband had a few lesions and reacted only slightly. Similar lesions developed in two children who were overnight guests, and the children reacted severely.

The mother consulted six physicians including three dermatologists, but was unsuccessful in obtaining a correct diagnosis. She had been treated with topical and systemic administration of steroids and had transitory relief. The patient strongly suspected that an unidentified arthropod was the cause of her pruritus and reported that on one occasion the pruritus had been more severe after her cat had shared her bed. Additionally, on more than one occasion, pruritus and papular formation began within about 30 minutes after she had held her cat. Scabies had been ruled out but flea bites and hives were still being considered in the differential diagnosis when a medical entomologist (R.S.L.) was contacted for assistance on March 21, 1985.

The asymptomatic cat had been treated with a bath of 0.06% pyrethrins and 0.6% piperonyl butoxide (Theradex) without apparent success. Two of us (R.S.L. and S.P.S.) subsequently examined the cat for *Cheyletiella* mites by first treating it with a pyrethroid wash, 0.05% tetramethrin (Aqua-Methrin), and then brushing it with a toothbrush along the spine and on both flanks anteriorly to the neck and posteriorly to the base of the tail. The brushing was examined in the laboratory (by R.S.L.) and 16 mites, identified as *C blakei*, were found. The specific identification was confirmed by Professor Deane P. Furman, University of California, Berkeley.

The cat was treated three times at weekly intervals with 8% methylcarbamate (Sendran), but the owner of the cat still reported some pruritus, though it was reduced appreciably. Further treatment of the cat by M.R. Floyd, DVM, using 0.15% pyrethrins and 1.5% piperonyl butoxide (Para Pyrethrin Mist) finally ended the complaint.

Two other Persian cats at the pet shop, one of which had been treated earlier with a lime-sulfur dip, were examined by one of us (R.S.L.) for the presence of mites. None was recovered from the brushings obtained from these cats. The treated cat had been suspected of haboring mites because it had scabs across its head and along its back. Moreover, lesions developed on one of the wrists of an employee of the shop who had previously brushed the cats.

Discussion

Human cheyletiellosis due to *C blakei* is a prime example of a cryptic arthropod infestation whose resolution is commonly arrived at circuitously even when mites are suspected as the cause. Methods used to ascertain the cause of this acariasis have either failed or achieved success after varying periods of delay. Here we present what we believe to be a more efficient, direct approach to the investigation of suspected cheyletiellosis, preceded by a brief review of the epidemiology, diagnosis and treatment of the disease.

Epidemiology and Diagnosis

Existing data suggest that *C blakei* is probably cosmopolitan in distribution,[11] is host-specific on cats[11] and completes its entire life cycle on cat fur and skin.[12] Its life away from its host (on humans or in the environment) is transitory. The possibility that free-living *C blakei* may occasionally cause dermatitis in susceptible persons cannot be discounted. Lesions may develop in casual visitors to a home having an infested cat without having direct contact with the cat either before the animal is treated or for a brief period afterward.[12] This possibility is suggested indirectly by a case involving *C yasguri* in which a child had hundreds of pruritic lesions after it had slept on a quilt used by an infested dog[13] and, in another case, when the same mite was recovered from the floor, furniture and a mattress.[14]

There appears to be no authoritative explanation of how human skin lesions due to *C blakei* are produced. In some instances, however, the distribution of skin lesions on the trunk and other body regions is noted to coincide with areas in contact with the infested cat. This observation suggests that the lesions are caused by bites of the mites.

Not surprisingly, once an etiologic agent is recognized, reports of its occurrence increase. Bjarke and co-workers[8] saw 37 cases of human cheyletiellosis in a two-year period. In California, canine and feline cheyletielloses are being seen with increasing frequency.[10] The true incidence of the disease in humans and pets in this state (and elsewhere in the western United States) is not known, but it is probably not as uncommon as suggested by the dearth of reports from this region.

Patients usually are of little help in providing information on the probable source of their dermatitis. Bjarke and associates[8] in referring to human cheyletiellosis said that among 37 patients in 24 homes "only in two cases did the owners themselves suspect their dogs or cats as being the indirect cause of their itching dermatitis." Thus, patients would very likely seek the help of a physician first rather than a veterinarian.

If *C blakei* is not suspected as the cause of dermatosis in humans by either a physician or a veterinarian,[3,15] cheyletiellosis may go undiagnosed or be attributed to delusions of parasitosis or to other causes. In the present case, scabies could have also been easily ruled out because the patient reported remission of her symptoms when she traveled abroad. Not infrequently, examination of lesions on the patients or their distribution on the body have led to suspicions or assertions that the complaints were due to some unspecified arthropod,[5,6,15] were due to hives[7] or were not caused by *Cheyletiella*.[16] In other cases, the dermatitis was mistakenly attributed to, or was suspected of being caused by, fleas on the pet.[9,10,15] Scraping the skin of a patient to obtain mite specimens is ineffective because the mites are not there for long, the unusual record of *C blakei* recovery from skin notwithstanding.[17] Inexplicably, *Cheyletiella* species has also been obtained from shakings from underclothes belonging to a woman who had no known contact with pets.[18]

In humans, pruritic lesions caused by *C blakei* are normally distributed on the anterior trunk, arms and legs—that is, often matching those parts of the body in contact with a cat when held.[3,5,8] In one case, the lesions occurred on the legs of a patient as a result of a cat having slept at the foot of the bed.[1]

Helpful information that could be obtained while interviewing patients suspected of having cheyletiellosis is whether remission of the dermatitis occurs when the patient is away from home[17] and whether the complaint began after the

cat was acquired[3,9] and subsequently became more severe after they handled it[5,9] or shared a bed with it.[4] Notably, not all persons in an infested household or in close contact with an infested cat are affected.[5,17]

While many infested cats are asymptomatic,[11] others have varying amounts of scale and may scratch themselves.[4,5,11,19] The cats we saw exhibited no gross lesions, visible flakings on the skin or fur or dandruff. The percentage of cats found to be infested with *C blakei* has varied in different studies, but reported infestation rates are typically low, such as 0.16% to 16.7%.[20-22]

The presence of *C blakei* has been established by the recovery of this mite in dust samples taken from the dust bag of a vacuum cleaner,[6] brushings[3,6,9,12,15,23] or combings[5] from fur, in cat feces[24] or in skin scrapings from cats.[9] These procedures are more likely to be undertaken if it is suspected that a cat is the source of the complaint or at least that an arthropod is the probable etiologic agent.

Treatment

Cats have been successfully treated with a number of different pesticides including DDT,[4,5,17] derris,[4] malathion,[19,23] Mycodex with carbaryl,[10,25] ronnel,[6] lime-sulfur dip,[10,25] methylcarbamate[9,24] and pyrethrins.[19] Our experience in observing the effects of pesticide treatments is too limited to recommend any of them therapeutically except for 0.15% pyrethrins (synergized with 1.5% piperonyl butoxide) and ronnel, which yielded satisfactory results in the present study and in an earlier one,[6] respectively. Because cats are known to be adversely affected by certain pesticides,[11] treatment of a cat should ideally be made by or under the supervision of a veterinarian. Following elimination of *C blakei* from cats, the disease in humans is self-limiting.

Detecting Mites on Cats

To determine the cause of canine scabies, flea or bedbug infestations and the like, as well as cryptic arthropod infestations affecting humans, medical entomologists rely mostly on investigative skills to recover the etiologic agents. These investigations usually involve examining the premises, suspected animal hosts and other potential sources of insects and mites. When the arthropod causing the complaint is found and identified, the corrective measure is often straightforward. Medical entomologists ordinarily contribute little, if any, authoritative clinical information useful for differential diagnosis.

When cats are suspected of harboring *C blakei*, we recommend that they be examined by placing them on a piece of white paper, treating them with a pesticide containing quick-knockdown components, such as pyrethrins synergized with piperonyl butoxide, brushing them and inspecting the brushings in 80% ethanol with a binocular microscope. Mites on paper are not readily apparent but when the brushings are placed in 80% alcohol, mites will float to the surface and are visible to the naked eye. This procedure was followed in each of the California cases mentioned above. In each case, the mites were found on the first brushing by the attending medical entomologist. Mites are commonly prepared for critical examination by clearing them in a suitable solution, such as Nesbitt's, and by mounting them in a medium such as Hoyer's in a slide preparation. Although mineral oil may be used as a temporary medium for slide preparation, it permits only gross examination of the mites. Attaching the mites to transparent, cellulose adhesive tape risks damage to them when they are later removed to prepare them for scientific study. If they are to be sent to a medical entomologist (or acarologist) for examination, they should be preserved in 80% alcohol. Several mites should be sent to increase the likelihood of having both sexes available for diagnostic purposes and to detect the possible existence of multiple mite-species infestations.

Information that should accompany specimens are the locale, date of collection, vertebrate host and collector's name. A brief description of the complaint is also desirable. Accumulation of these kinds of data will eventually result in better understanding of the biology of this pestiferous mite.

If a physician, by a combination of clinical evidence and response to questions, is able to establish with reasonable certainty that the dermatitis is due to *C blakei*, then treatment of the cat with an appropriate pesticide is indicated. On the other hand, if an unknown arthropod is suspected as the cause of the dermatitis, then we recommend that the case be referred to a medical entomologist for follow-up investigation. In California and other western states, medical entomologists knowledgeable about parasitic mites may be contacted through some universities, university extension services or health departments.

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A Program to Provide Hepatitis B Immunoprophylaxis to Infants Born to HBsAg-Positive Asian and Pacific Island Women

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Between January 1, 1984, and December 31, 1985, there were 545 women from Asia and the Pacific Islands who gave birth to a total of 572 infants at Highland General Hospital in Oakland, California (accounting for 20% of all deliveries at that hospital). For countries having more than ten women giving birth during the study period, the percentage of women screened prenatally for HBs antigen (Ag) ranged from a high of 100% (Laos) to a low of 54% (Philippines). HBsAg-positivity rates ranged from a high of 21% (Tonga) to a low of 0% (India). A total of 52 infants was born to 49 HBsAg-positive mothers, and 40 (77%) of the infants received hepatitis B immune globulin (HBIG) within 12 hours of birth. While 80% of the infants received HBIG and at least one dose of hepatitis B vaccine, only 35% received the recommended schedule of HBIG and three doses of vaccine.

(Klontz KC: A program to provide hepatitis B immunoprophylaxis to infants born to HBsAg-positive Asian and Pacific Island women. West J Med 1987 Feb; 146:195-199)

Mother-to-infant transmission of hepatitis B virus (HBV) plays a major role in maintaining high infection rates of hepatitis B within many Asian populations. For example, in Taiwan, 5% to 20% of the population are HBs antigen (Ag) carriers,[1] and it is estimated that as many as 35% to 50% of these carriers are infected perinatally by their mothers.[2]

Studies have shown that the rate of development of the HBV carrier state in infants born to mothers positive for HBsAg may be reduced by as much as 80% to 90% with the timely use of hepatitis B immune globulin (HBIG) and hepatitis B vaccine.[3-5] Such efficacy is notable in light of the fact that HBsAg carriers have significantly higher rates of cirrhosis and hepatocellular carcinoma than noncarriers.[6]

Since 1981, the Immunization Practices Advisory Committee (ACIP) has issued a series of revised recommendations aimed at preventing mother-to-infant transmission of hepatitis B.[7-10] Current ACIP guidelines recommend (1) that mothers belonging to groups at high risk of acquiring or transmitting hepatitis B infection (including women of Asian or Pacific Island descent) be tested routinely for HBsAg during the prenatal period; (2) that all infants born to HBsAg-positive women receive hepatitis B immune globulin (0.5 ml intramuscularly) after physiologic stabilization and preferably within 12 hours of birth and hepatitis B vaccine (0.5 ml [10 μg] intramuscularly) at birth and 1 and 6 months of age, and (3) that all infants receiving hepatitis B immunoprophylaxis be tested for HBsAg and anti-HBs at 12 to 15 months of age to monitor the success or failure of therapy.

Since 1975 more than 750,000 Southeast Asian refugees have entered the United States; nearly 40% of these new refugees have settled in California.[11] About 45% of Southeast Asian refugees are younger than 18 years, and 40% are female.[11]

The purpose of this study was twofold: to determine the extent to which Asian and Pacific Island women delivering at a county hospital in Alameda County were screened prenatally for HBsAg during the time period 1984-1985, and to ascertain the timing of HBIG and hepatitis B vaccine administration to those infants born to HBsAg-positive mothers.

Patients and Methods

The study cohort was selected by using birth certificates filed at the Office of Vital Registration, Alameda County Health Care Services Agency. Birth certificates were reviewed for all infants born at Highland General Hospital (Oakland, California) in the two-year period, January 1, 1984, through December 31, 1985. The following information was obtained from the birth certificates: country of birth and name of the mother and name and date of birth for each infant.

Information gained from the birth certificates was used to compile a list of the names of all mothers born in Asia or the Pacific Islands who were delivered of an infant at Highland General Hospital in 1984-1985. Medical records were reviewed for the results of prenatal HBsAg screening. Medical records were then reviewed for those infants born to HBsAg-positive Asian or Pacific Island mothers to determine if and when HBIG and hepatitis B vaccine were administered.

Highland General Hospital is a county-operated 260-bed acute care hospital. The hospital serves as the site of delivery

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ABBREVIATIONS USED IN TEXT

ACIP = Immunization Practices Advisory Committee
Ag = antigen
HBIG = hepatitis B immune globulin
HBV = hepatitis B virus

for the women who receive their prenatal care at the hospital itself and for many women who are seen prenatally at one of the various county and community clinics. The infants in this study who were born at Highland General Hospital received postnatal care at either the hospital pediatrics clinic or at one of the other county or community clinics.

Since 1981 Highland General Hospital has participated as one of several San Francisco Bay Area hospitals in an ongoing New York Blood Center study of an experimental recombinant hepatitis B vaccine. As part of the New York Blood Center study, women born in Asia or the Pacific Islands who gave birth at Highland General Hospital have been screened prenatally for HBsAg and HBeAg. To be included in the New York Blood Center trial, an infant delivered at Highland General Hospital had to be born to a mother who was positive for both HBsAg and HBeAg. These infants have been given the experimental vaccine by health care workers who visited the infants at their homes (Hooi Yeap, RN, San Francisco General Hospital, oral communication, October 1985).

Infants born to HBsAg-positive, HBeAg-negative mothers were not included in the New York Blood Center trial. Instead, these infants were treated in a program sponsored by the Alameda County Health Care Services Agency. In this program, the infants received the currently licensed plasma-derived hepatitis B vaccine (0.5 ml [10 μg] given intramuscularly at birth and at 1 and 6 months) in hospital or at one of the county or community clinics. All infants born to HBsAg-positive mothers, regardless of whether they were in the New York Blood Center trial or in the Alameda County Health Care Services Agency program, were supposed to have HBIG (0.5 ml intramuscularly) administered to them at birth by hospital personnel.

Because the intent of the study reported here was to determine the effectiveness of the perinatal hepatitis B-prevention program administered by the Alameda County Health Care Services Agency, the analysis of hepatitis B vaccine use in this study excludes those infants enrolled in the New York Blood Center trial.

Medical records of all infants born to HBsAg-positive mothers were reviewed at Highland General Hospital to determine how many doses of vaccine were administered; if fewer than three vaccine doses were noted in the hospital medical record, a check was made to determine whether the infant received any vaccine at the clinic where the mother received her prenatal care. More than six months was allowed to elapse following the birth of an infant before that infant was classified as having had a given number of doses of vaccine.

Results

Between January 1, 1984, and December 31, 1985, a total of 545 women from Asia or the Pacific Islands were delivered at Highland General Hospital of 572 infants (5 mothers gave birth to twins, whereas 22 mothers were delivered of single infants on two different occasions during the study period). The 572 infants accounted for 20.0% of all infants born at the hospital during the two calendar years (572/2,866).

For the 545 women who gave birth at Highland General Hospital in 1984-1985, Table 1 shows, by country of birth, the results of the hepatitis B screening.

A total of 52 infants was born to the 49 HBsAg-positive mothers in this study. Figure 1 shows the time schedule when the 52 infants received hepatitis B immune globulin: 25 of the infants (48%) received HBIG within 2 hours of delivery, 40 infants (77%) had HBIG administered within 12 hours of birth, 7 infants (14%) received HBIG more than 12 hours after birth, while 5 infants (10%) received no HBIG.

Figure 2 summarizes the vaccine schedule for the infants born to HBsAg-positive mothers. In all, 12 infants were excluded from the analysis because of their participation in the New York Blood Center trial. Thus, of the 40 infants remaining in the Alameda County Health Care Services Agency program, 14 (35%) received three doses of vaccine, 10 (25%) received two doses, 10 (25%) received one dose and 6 (15%) received no vaccine.

Of the 40 infants, 6 were born to mothers who were positive for both HBsAg and HBeAg; the mothers of these 6

TABLE 1.—*Results of Hepatitis B Screening of Asian and Pacific Island Women Giving Birth at Highland General Hospital, 1984-1985*

Country	Women Giving Birth, No.	Screened, No. (%)	HBsAg Pos No. (%)	HBeAg Pos No. (%)
Cambodia . . .	137	135 (99)	11 (8)	3 (2)
Vietnam	101	96 (95)	7 (7)	3 (3)
Laos	100	100 (100)	13 (13)	4 (4)
Philippines . .	59	32 (54)	1 (3)	0 (0)
China	55	53 (96)	10 (19)	3 (6)
Tonga	38	29 (76)	6 (21)	5 (17)
Korea	17	15 (88)	1 (7)	0 (0)
India	11	8 (73)	0 (0)	0 (0)
Others*	27	16 (59)	0 (0)	0 (0)
Totals	545	484 (89)	49 (10)	18 (4)

Pos = positive

*Samoa, Fiji, Guam, Japan, Malaysia, Indonesia, Thailand, Singapore, Burma

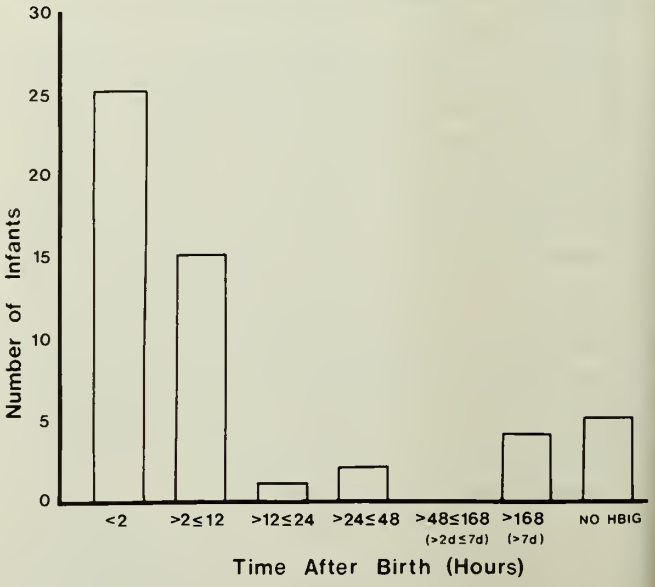

Figure 1.—Schedule of administration of hepatitis B immune globulin (0.5 ml intramuscularly) given to infants born to Asian or Pacific Island HBsAg-positive women, Alameda County, 1984-1985.

infants were inadvertently excluded from the New York Blood Center trial. The average number of doses of vaccine given to infants born to HBeAg-positive carrier mothers (average 2.0 doses) did not differ significantly from the average number of doses given to infants born to HBeAg-negative carrier mothers (average 1.8 doses).

Table 2 summarizes the hepatitis B prophylaxis administered to the 40 infants born to HBsAg-positive mothers. While 32 infants (80%) received HBIG and at least one dose of hepatitis B vaccine, only 14 (35%) of the infants received the recommended schedule of HBIG plus three doses of vaccine. There were no significant differences in the extent of treatment administered to those infants born in 1984 compared with the group of infants born in 1985.

Discussion

Mother-to-infant transmission of hepatitis B virus among Asians and Pacific Islanders is an important issue in many areas of the United States for two reasons. First, these two population groups have high HBsAg carrier rates and are therefore at risk of infecting their infants during the birth process. Second, a significant number of Asian refugees has arrived in the United States since 1975, thereby directly adding to the population cohort at highest risk for mother-to-infant transmission of HBV. As of September 30, 1984, there were eight states that had more than 20,000 Southeast Asian refugees in residence (Table 3).

Highland General Hospital cannot be considered a typical county hospital with respect to its perinatal hepatitis B program, as the hospital has been a participant during the past five years in an ongoing trial of an experimental hepatitis B vaccine. As a result, health care personnel are likely to have been much more aware of the need for prenatal screening of women from Asia or the Pacific Islands.

There are several factors, however, that make Highland General Hospital similar to other county hospitals. For example, the hospital serves a predominantly uninsured population, representing numerous different races and nationalities.

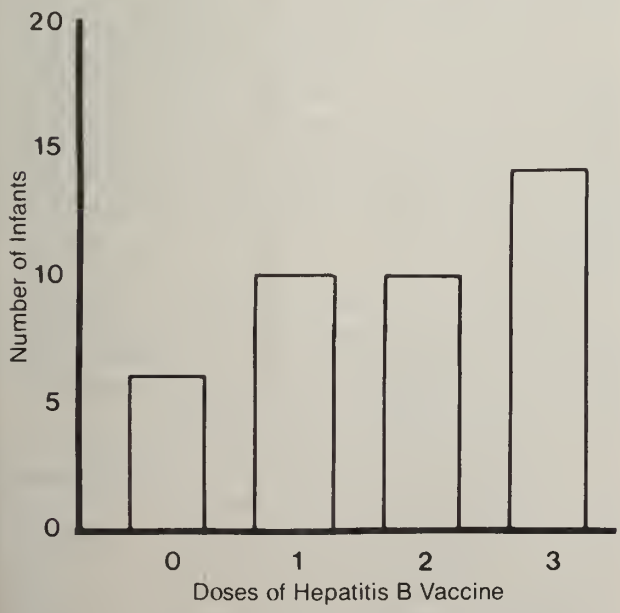

Figure 2.—Number of doses of hepatitis B vaccine (0.5 ml [10 μg] intramuscularly) administered to infants born to Asian or Pacific Island HBsAg-positive women, Alameda County, 1984-1985.

Many of the women who present to the hospital do so with late or no prenatal care. A significant proportion of the women who give birth at Highland General Hospital are subsequently lost to follow-up, and it is often difficult to monitor the health of the infants born to such women.

Four areas are discussed concerning Alameda County's perinatal hepatitis B prevention program: screening of women, treatment of infants born to HBsAg-positive mothers, costs of administering the program and recommendations for increased program effectiveness.

Screening

Of the eight countries having more than ten women giving birth at Highland General Hospital in 1984-1985, prenatal screening exceeded 80% for six; pregnant women born in the Philippines and Tonga were screened less frequently.

Two explanations may partially account for the relatively infrequent screening of women from the Philippines. First, because Filipinos generally speak English well, it may be that some health care workers assume such women to be from the United States. Second, the Hispanic surnames of many Filipinos may incorrectly suggest to some that these women are from Latin-American nations. Nevertheless, it is important to test this population group prenatally for HBsAg status; in their study of the prevalence of HBsAg in pregnant Asian-American women by country of birth, Stevens and co-

TABLE 2.—*Hepatitis B Prophylaxis Administered to Infants Born to Asian and Pacific Island HBsAg-Positive Mothers, Alameda County, 1984-1985 (N=40)*

Treatment	*Infants, No.*		*Percent of Total Infants Born to HBsAg-Pos Mothers*	
HBIG and vaccine		32		80
HBIG + 1 dose vaccine	9		23	
HBIG + 2 doses vaccine	9		23	
HBIG + 3 doses vaccine	14		35	
HBIG only		3		8
Vaccine only		2		5
1 dose	1		3	
2 doses	1		3	
3 doses	0		0	
Nothing		3		8
Totals		40		101

HBIG = hepatitis B immune globulin, HBsAg-Pos = positive for HBs antigen

TABLE 3.—*Estimated Southeast Asian Refugee Population By State—September 30, 1984**

State	*Southeast Asian Refugees, No.*
California	285,100
Texas	51,300
Washington	32,600
New York	24,800
Illinois	23,400
Pennsylvania	23,900
Minnesota	22,600
Virginia	21,000
Total 8 states	484,700
Total United States	711,000

*From Report to the Congress, January 31, 1985: Refugee Resettlement Program, Office of Refugee Resettlement, US Department of Health and Human Services.

workers found 5% of women from the Philippines to be positive for HBsAg.[5]

The observation that only 77% of the women from Tonga in this study were screened prenatally for HBsAg is important given their significant carrier rate of both HBsAg and HBeAg.

In general, in most of the instances where prenatal screening for HBsAg failed to occur, the women involved came to Highland General Hospital with either little or no prenatal care. This observation is based on the date in a woman's medical chart that states when prenatal care was begun. All women, however, regardless of how much prenatal care they had received, were tested for rubella titer and hematocrit before delivery. Thus, even though blood was drawn on all women prenatally, it appears that the HBsAg assay was omitted in some instances because of failure to recognize the women involved as being at high risk for transmitting HBV.

Treatment

The efficacy of a perinatal hepatitis B treatment program depends on administering HBIG on the same day an infant is born, and preferably within 12 hours of birth.[10]

In this study, while 32 of 40 infants (80%) received HBIG at birth and at least one dose of vaccine, only 14 infants (35%) were given the full recommended course of three doses of vaccine. Of the 26 infants who received less than the recommended course of vaccine, 1 was reported to have left the area; the remaining 25 infants are presumed to have either left the area without the knowledge of their primary care provider or simply to have been lost to follow-up despite still residing in the area. It is also possible that some of the infants received doses of hepatitis B vaccine at clinics or physicians' offices outside of the county health care system (this is not likely to have occurred frequently, given that the mothers in this study relied on county medical resources for much of their health care needs).

Of the 25 infants who received less than the recommended regimen of immunoprophylaxis, 21 were born to HBeAg-negative women, while the remaining 4 had HBeAg-positive carrier mothers. Though no serologic follow-up results are available, there is a high probability that few if any of the infants born to HBeAg-negative carrier mothers became HBsAg-positive because HBeAg-negative mothers rarely transmit HBV to their infants in the perinatal period.[10] The four infants born to the HBsAg-HBeAg-carrier mothers, however, had a greater risk of becoming infected, based on the observation that 70% to 90% of untreated infants born to HBsAg-HBeAg-positive mothers are infected perinatally.[10] One of these four infants received only HBIG at birth and no vaccine.

Costs

The costs incurred in a program of preventing mother-to-infant transmission of hepatitis B include the cost of screening women prenatally for HBsAg, the cost of administering HBIG and vaccine to those infants born to HBsAg-positive mothers and the cost of testing the treated infants for HBsAg and anti-HBs at 12 to 15 months of age.

For the two-year period encompassed in this study, the cost of the perinatal hepatitis B prevention program amounted to about $8,200. This figure is based on the following costs reported by the hospital pharmacy and contracting laboratory: $12 per HBsAg assay entailed in screening women prenatally, $16 per dose (0.5 ml) of HBIG and $23 per dose (0.5 ml) of hepatitis B vaccine administered to the infants born to HBsAg-positive women.

There are several reasons why the figure $8,200 understates the true costs that would have accrued had the prophylaxis program been more comprehensive. First, 61 women from Asia and the Pacific Islands were not screened prenatally for HBsAg. Second, only 35% of the infants born to HBsAg-positive women received the recommended regimen of HBIG and vaccine. Finally, no routine testing at 12 to 15 months for anti-HBs and HBsAg was done in those infants who received the recommended regimen of immunoprophylaxis.

Recommendations for Increasing Program Effectiveness

The goal of a perinatal hepatitis B prevention program is twofold: to identify HBsAg-positive women prenatally and to administer appropriate immunoprophylaxis to the infants born to carrier mothers.

The results of this study suggest several areas at the screening and treatment levels where program effectiveness might be enhanced.

Screening. The primary goals during the prenatal period should be determination of the HBsAg status of all Asian and Pacific Island women (both refugee/immigrant and US-born) and communication of these results to patients and appropriate health care workers. Specifically, the following recommendations are offered:

1. Health care workers involved in providing prenatal care to Asian and Pacific Island women should be informed about the high HBV carrier rates characteristic of these population groups and the need to routinely screen these women prenatally for HBsAg.

2. Every woman who tests positive for HBsAg during the prenatal course should be advised about the results. She should be informed about the potential for mother-to-infant transmission of virus and about the need for her infant to receive proper immunoprophylaxis. Because many Asian refugees may not understand English, appropriate interpreter resources should be available.

3. When a woman is identified as HBsAg-positive during the prenatal period, a system should be in place whereby the results of the positive test become known to the following health care providers: the hospital obstetric and pediatrics services, the hospital infection control nurse, the pediatrics clinic where the infant will receive posthospital care and the appropriate county public health personnel. To facilitate such a chain of communication, the following recommendations are offered:

- The woman's medical chart should be labeled in a manner that clearly notifies the hospital obstetric service of the HBsAg-positivity. Upon delivery, the infant's medical chart should be labeled to notify the pediatrics service that the baby was born to an HBsAg-positive mother.
- The infection control nurse at the hospital where delivery is planned should be notified of all HBsAg-positive women identified during the prenatal period. The infection control nurse could then ensure both that the obstetric service is aware of the HBsAg-positivity before delivery and, after delivery, that the infant receives proper immunoprophylaxis.
- Because a significant proportion of Asian and Pacific Island refugees take their infants to county-supported pediatrics clinics after being discharged from hospital, personnel in

the county communicable disease control office should also be notified of all prenatal HBsAg-positive results. Appropriate county public health personnel could then follow up on the infants to ensure that they receive the second and third doses of vaccine and the postimmunoprophylaxis serologic testing at 12 to 15 months.

Treatment. The primary goals of treatment are to ensure that all infants born to HBsAg-positive women receive the full recommended immunoprophylaxis and undergo serologic testing for HBsAg and anti-HBs at 12 to 15 months of age. Specifically, the following recommendations are offered:

1. The hospital obstetric service should have a protocol that clearly defines how an infant born to an HBsAg-positive mother is to receive HBIG and hepatitis B vaccine. Where pediatric and obstetric services overlap, the protocol should define which service has the responsibility for administering the immunoprophylaxis.

2. The hospital infection control nurse, notified during the prenatal course of a mother's positive HBsAg status, should ensure that each infant born to an HBsAg-positive mother receives HBIG and the initial hepatitis B vaccine before discharge from hospital.

3. The infection control nurse or the pediatrics service should notify the county public health personnel where follow-up pediatric care is planned for each infant born to an HBsAg-positive mother. This should be done at the time of discharge or shortly thereafter. County personnel (such as a public health nurse) could then follow up on each child to ensure that the second and third doses of vaccine are administered and that proper serologic testing is done on the infant at 12 to 15 months of age.

Conclusions

To determine the effectiveness of existing perinatal hepatitis B prevention programs, the health care community should continue to assess regularly the prenatal screening of pregnant women from Asia and the Pacific Islands and the appropriate use of hepatitis B immunoprophylaxis for the infants born to these women. This study has shown how such an assessment may reveal that a significant number of infants born to HBsAg-positive mothers in a given program are receiving less than the recommended treatment of hepatitis B prophylaxis.

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Medical Progress

Physical Activity and Health Maintenance—Exactly What Is Known?

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Broad claims have been made regarding the health benefits of physical activity. In analyzing the data on which these claims are based, including those on the risks of exercise, 5 of 13 proposed health benefits were found to have strong support in the literature. For the remainder the evidence is less conclusive or equivocal. Data regarding the risks of exercise are similarly varied. Proponents of physical activity should evaluate the documentation of its benefits and risks so as not to dilute the power of their remedy with unsubstantiated claims.

(Phelps JR: Physical activity and health maintenance—Exactly what is known? West J Med 1987 Feb; 146:200-206)

Despite the current vogue that exercise now seems to enjoy, recent estimates of physical activity in the United States indicate that at least 40% of our population is completely sedentary, and only 20% exercises with an intensity and frequency generally recommended for cardiovascular benefit.[1] Yet exercise has been proclaimed to have lipid-lowering, antihypertensive, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and antidepressive qualities, among others.[2] Is the majority of the American populace missing out on a miracle drug?

In previous overviews of the benefits and risks of exercise,[3,4] the quality of the data on which these claims are based has not been critically assessed. This report is a comprehensive evaluation of that data, which shows that many of the proposed benefits have little or no substantiation in the literature. To sharpen the focus on physical activity and health maintenance, only work involving healthy persons has been considered. Discussion of exercise as a therapeutic tool, such as in the treatment of diagnosed hypertension, obesity, diabetes mellitus or mental illness, can be found in most of the respective review articles cited herein.

Surety Rating

At the close of the discussion of each proposed benefit and risk of physical activity, an index of the surety that the literature allows is provided. This rating is a subjective judgment based on the data presented. It is designed to facilitate comparison of the support each claim enjoys. Readers are encouraged to review citations of interest and arrive at their own judgments. Ratings are based on the following scale:

0 = data are mixed; no point of view is favored;

1+ = most data are supportive but a significant fraction of reports (significant either in number or quality of results) does not support the claim;

2+ = established; little or no conflicting data.

The results of this rating process are presented in Table 1, which also serves as an index to the sections that follow.

Exercise Benefits

Blood Pressure

Exercise clearly has a role in the treatment of diagnosed hypertension.[5] But does physical activity help maintain normotension? This concept is suggested by observations that the age-associated increase in blood pressure characteristic of most modern societies[6] is not seen in more physically active societies such as the Kalahari bushmen.[7] Investigations of this relationship include cross-sectional studies of work-associated and leisure-time activities, longitudinal studies during exercise programs and epidemiologic cohort studies.

No consistent association between work-associated activity and blood pressure has been shown.[8,9] In contrast, leisure-time activity[9] and treadmill performance[10,11] (an indicator of physical fitness, presumably reflecting habitual physical activity) are inversely correlated with systolic and diastolic blood pressures. Moreover, longitudinal experiments with normotensive subjects have repeatedly shown decreases in blood pressure following exercise training programs.[5]

These studies have been supplemented by two recent cohort studies in which groups of subjects whose blood pressure was known in the past were reassessed for current blood pressure; changes in pressure over time were compared with the subjects' reported physical activity[12] or treadmill-tested fitness.[13] These investigations show that a sedentary life-style is associated with a 35% to 52% greater likelihood of hypertension developing compared with the physically active populations.

Overall these various reports suggest that leisure-time physical activity does indeed help maintain blood pressure within the normal range. Work-associated activity appears to lack the quality required to produce this effect. Surety rating 2+.

Serum Lipid Levels

Cholesterol carried by low-density lipoprotein (LDL-C) has been consistently associated with the risk of coronary

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ABBREVIATIONS USED IN TEXT

EEG = electroencephalographic
HDL-C = high-density-lipoprotein cholesterol
LDL-C = low-density-lipoprotein cholesterol

heart disease and that carried by high-density lipoprotein (HDL-C) with reductions in risk.[14] Considerable research has been devoted to defining the effects of regular physical activity on these serum lipoproteins.

Endurance athletes have lower LDL-C levels than sedentary controls in roughly two thirds of reports on this select group of subjects, but comparison between active and inactive members of the general population does not show this difference.[15] Reductions in LDL-C levels following exercise training programs have also not been consistently found.[16]

Associations of higher HDL-C levels with habitual exercise have been much more consistent, but numerous studies have shown conflicting results.[17] Prospective studies examining the effect of exercise training programs on HDL-C levels have also yielded conflicting results.[16] A recent well-designed longitudinal study, however, showed that changes in HDL-C values during exercise training were correlated ($P = .0008$) with the amount of exercise regularly performed.[18] Much of the inconsistency in the data regarding exercise and HDL-C levels may be explicable on the basis of difficulties in quantifying the amount of physical activity actually pursued by study participants.

At this time, however, the data on exercise and serum lipoproteins remain mixed. There is more support for exercise-induced changes in HDL-C levels than those of LDL-C. Surety rating 1+.

Smoking

Does physical activity help persons to avoid taking up smoking or help them quit once they have begun? Numerous studies of various designs have addressed this question.

Studies using questionnaires to assess physical activity and smoking behavior generally report an inverse relationship between these pursuits.[19] Several show a positive association between work-related physical activity and smoking, which again underlines the importance of distinguishing between work- and leisure-time physical activities. Treadmill-tested fitness is consistently inversely correlated with smoking behavior—that is, more physically fit persons, as defined by treadmill performance, smoke less.[10,20,21] Smoking itself, however, decreases treadmill performance through its effect on respiratory function,[22] so that those who smoke would be expected to appear less physically fit and, by implication, less physically active.

Longitudinal studies in exercise training programs have not shown a change in smoking behavior as untrained persons begin regular exercise.[23,24] These studies, however, were plagued with nonadherence to the exercise program; in one report the dropout rate for smokers was nearly twice that for nonsmokers.[24] Thus smoking behavior appears to be an effective predictor of exercise adherence, but conclusions regarding the converse cannot be drawn from these data.

Finally, results of a smoking history questionnaire administered to a group of 1,423 runners revealed that only a small percentage (15%—less than half the US average[25]) smoked before they began running,[26] which is consistent with the results of the longitudinal studies. Within this small group 81% of the men and 75% of the women stopped smoking when they began running.

It appears that the strong inverse correlation between exercise and smoking behavior may be largely due to a selection effect—smokers undertaking exercise programs less frequently than nonsmokers—rather than an effect of exercise itself. No conclusion on this issue is possible based on the available data. Surety rating 0.

Weight Control

The danger of obesity per se is not clear when a person exceeds ideal weight by less than 20% to 30%.[27] Because becoming obese clearly has an impact on psychological well-being,[27] however, and because cardiac risk factors such as hypertension, hyperlipidemia and diabetes are associated with weight gain,[14] it is reasonable to ascribe health benefits to physical activity if it can lower the risk of becoming obese.

The contribution of physical activity to total daily caloric expenditure is relatively small: if strictly adhered to, the minimum exercise program currently recommended[28] adds roughly 1,000 kcal per week to a sedentary person's weekly outlay of 14,000 kcal, only a 7% increase. The pattern of weight gain in the United States, however, is a slow but steady increase with age.[25] Such an increase can be produced

TABLE 1.—*Benefits and Risks of Physical Activity*

System	Benefit	Surety Rating	Risk	Surety Rating
Cardiovascular	Blood pressure control	2+	Cardiac arrest	2+
	Improved serum lipid profile	1+		
	Smoking cessation/prevention	0		
	Weight control	2+		
	Independent effect	2+		
Psychological	Improved affect	1+	Exercise addiction	1+
	Increased self-esteem	2+		
	Positive personality change	0		
	Improved cognition	0		
Musculoskeletal	Prevention of postmenopausal bone loss	2+	Amenorrhea/bone loss	2+
			Trauma	2+
CNS	Improved sleep	0		
Endocrine	Decreased risk of diabetes	0	Decreased libido	0
GI tract	Increased colonic motility	0	Diarrhea	1+

CNS = central nervous system, GI = gastrointestinal

by a very small disparity between caloric intake and expenditure: consuming an excess of a mere 10 kcal per day leads to a 1-lb weight gain per year.[29] Clearly then, even a minimal program of physical activity added to the life-style of a sedentary person could protect against weight gain.

The foregoing analysis, of course, assumes that caloric intake remains constant. The question of whether increased caloric expenditure triggers increased caloric consumption has been studied since the 1950s and is still debated.[30] No day-to-day correlation between caloric output and intake has been shown, and most studies have shown a slight decrease in caloric consumption when physical activity increases, though these studies have been largely observational, not experimental.[31] Two recent truly experimental studies both show that caloric intake does not increase when obese subjects begin an exercise program,[30,32] and one reports a significant decrease in consumption equivalent to that during an imposed diet.[30] Unfortunately there are no similar studies available in non-obese subjects.

Finally, much has been made of the repeated observation that the basal metabolic rate remains elevated after an exercise period.[30,31] There is no clear consensus on how long this elevation persists, but estimates range from a few hours to two days.[31] A recent well-designed study, however, failed to find any significant elevation of the basal metabolic rate following even intense exercise.[33]

Physical activity clearly shifts the caloric intake-output balance toward the negative by increasing expenditure during activity. Whether expenditure remains elevated following exercise, and whether exercise may also decrease caloric intake, has yet to be determined. Surety rating 2+.

Independent Effect

Physical activity may reduce the risk of cardiovascular disease through a reduction in risk factors, as detailed above. Some evidence suggests that physical activity may have an independent effect as well.

An inverse relationship between physical activity and the risk of coronary heart disease has been shown in a wide variety of epidemiologic studies.[12,34-37] This relationship is best shown in studies of leisure-time activity and is generally not seen in studies of work-associated activity alone.[34]

Multivariate analysis is required to adjust for differences in risk factors that covary with physical activity and could account for the relationship observed. Applied to the Framingham data, this technique showed an independent effect of exercise only in men, not in women.[37] But the Puerto Rico Health Program[38] and a study of Los Angeles fire fighters and police officers[39] both report that physical activity was inversely correlated with coronary heart disease risk after adjusting for differences in blood pressure, serum lipid levels, relative weight and the presence or absence of cigarette smoking.

Moreover, the latter study joins three others[40-42] that present strikingly similar data, suggesting that the protective effect of physical activity is more pronounced in the presence of other risk factors. These investigators found that when risk factor levels were high, the risk reduction attributable to exercise was also dramatically high. This held true for blood pressure, relative weight, cigarette smoking and family history of cardiovascular disease; the serum cholesterol level was not examined. Collectively these works show that the reduction in coronary heart disease risk due to physical activity may not only be independent of reductions in other risk factors but actually more powerful when those risk factors are present. Surety rating 2+.

Mental Health

One of the most widely proclaimed benefits of physical activity is its effect on mental health. A vast literature comprising more than 1,100 articles has been produced in the study of this phenomenon.[43] Experimental design, however, has generally been so inadequate in these studies that their usefulness is limited.[44-47] (In a search for well-designed, randomized, experimental studies, I was forced to reject all but 12 reports.[43]) Of the plethora of proposed mental health benefits,[44] only four major areas have been consistently examined: affect, self-esteem, personality and cognition.

Affect: mood, depression, anxiety. Studies of longitudinal design have consistently shown a positive effect of exercise on mood, depression and anxiety.[47] More recent studies have distinguished between state (temporary or transient) and trait (personality-based) anxiety and have generally shown that exercise is effective in reducing only the former.[46] Only five studies in this area meet strict experimental criteria, however, and, of those, only one showed a positive effect of exercise training.[43]

Proposed mechanisms for this mood-improving effect include a change in central nervous system monoamine metabolism[48]—a hypothesis that has some support from animal experimentation but is wholly untested in humans—and the so-called endorphin hypothesis.[49] Enthusiasm for the latter has waned since it has been shown in a double-blind crossover experiment that naloxone (an opiate antagonist) does not block the mood shift associated with running,[50] although it has been argued that the naloxone dose was inadequate.[49] Surety rating 1+.

Self-esteem. Of 13 studies, 11, including 4 that meet strict experimental criteria,[43] have shown improved self-esteem following exercise training.[47,51] Interestingly, the only two reports that failed to show such an effect did not use aerobic training programs.[47] It should be noted that of all the proposed health benefits of exercise, none has more unequivocal support than these findings on self-esteem.

For both affect and self-esteem, however, it remains entirely possible that the observed positive effects of exercise training programs are due to factors other than physical activity itself. None of the studies to date have effectively controlled for other proposed mediators such as an expectancy effect[46]; the experience of mastery[43]; an effect of mere cognitive diversion, allowing distraction[49] or simply "time out"[48] from belittling, depressing or anxiogenic circumstances, or learning to reinterpret somatic symptoms of anxiety.[43] Surety rating 2+.

Personality. There are few studies relating personality change and physical activity, and none shows unequivocal improvement. There is considerable evidence, however, that physical activity has both a psychological and somatic relaxation effect.[46] For example, 15 minutes of walking was shown to be a more effective muscle relaxant than 400 mg of meprobamate in elderly anxious subjects.[52] This has led to an examination of exercise as an adjunct means of altering the type A behavior pattern. Four recent studies (two published only in abstract) found a reduction in the physiologic or the psychometric (or both) correlates of type A behavior following exercise training.[46] Two others, however, found no such effect in

men who have had a myocardial infarction or in college women participating in aerobics programs.[44] Surety rating 0.

Cognition. Research on physical activity and cognitive function has been scattered among children, adults and geriatric populations. The physical activity regimens have varied widely. Moreover, there is far more variation than consistency in the psychological measurement tools used, such as Wechsler Intelligence Scales, arithmetic tasks, IQ tests and so forth. The data are therefore very difficult to interpret. In studies of both children and adults, the results are largely equivocal.[44] There is slightly more support for an association between physical activity and improved cognition in the elderly,[46,47] but there are contradictory reports of similar design. More research using standardized activity regimens and testing devices will be required to clarify this area. Surety rating 0.

Bone Density

Loss of bone density begins for most women in their fourth decade but becomes dramatic after menopause.[53] Those who have not adequately invested in their "bone bank" before this period of steady loss can eventually fall below a critical level of bone strength (fracture threshold) and become susceptible to vertebral, radial or femoral neck fractures.[54] Treatment of these fractures currently costs an estimated 3.8 billion dollars annually.[55]

Physical stress on bone is associated with changes in its form, a relationship long recognized and codified as Wolff's law.[56] This relationship and the natural history of postmenopausal osteoporosis lead naturally to the hypothesis that a woman might, by engaging in physical activity, be able to promote sufficient bone deposition to keep herself above the fracture threshold during postmenopausal bone loss.[57]

The hypothesis has not been directly tested, but considerable data exist to support it. In cross-sectional studies, Olympic athletes,[58] cross-country runners,[59] marathoners (male[60] and female[61]), ballerinas and weight-lifters[62] have been shown to have greater bone density than sedentary controls. Tennis players have greater bone density in their dominant arm, unless ambidextrous.[63] No studies failed to show such a relationship when comparing those who are regularly physically active with inactive subjects.

It has also been shown that in young adults protection from gravity by bed rest or space travel leads to bone loss,[64] and that this bone is regained when normal daily activity is resumed.[65] Prospective experimental studies have been done only in postmenopausal women[66-69]; all showed a small increase in bone density in the exercising group, whereas control groups experienced a steady decline. Unfortunately, there are no longitudinal studies in the population in question—that is, premenopausal women.

Thus, while the hypothesis that regular physical activity can lower the risk of postmenopausal osteoporosis has not been tested directly, evidence from various sources supports this concept. Surety rating 2+.

Sleep

Does increased physical activity improve the quantity or quality of sleep? The prevalence of sleep disorders and the complications that follow the pharmacologic therapy thereof make this an important question.

Despite the common belief that intense physical activity "makes you tired"—that is, more ready to sleep or inclined to sleep longer—electroencephalographic (EEG) data on sleep following various exercise conditions do not show such an effect. Of 17 EEG-monitored sleep experiments, none showed a difference between regular exercisers and sedentary persons in sleep latency, wakefulness during the night or total sleep time.[70-72] Similarly, there was no demonstrable effect of a short, intense bout of exercise on any of these variables.[73]

Interestingly, although fitness does not appear to affect objective assessments of sleep, a person's perception of the quantity and quality of sleep may be affected by regular physical activity. Fit subjects' sleep logs indicated a shorter perceived sleep latency and higher ratings of sleep quality compared with the reports of unfit subjects, according to the single available study of the subjective aspects of sleep.[71]

Proponents of physical activity should recognize that there is no objective evidence of improved sleep with regular exercise. Surety rating 0.

Diabetes Risk

Exercise has long been recognized as having beneficial effects in patients with diabetes mellitus,[74] possibly since as early as 600 BC.[75] Does physical activity play a role in preventing non-insulin-dependent (type II) diabetes mellitus as well? No experimental data address this question directly, but some laboratory studies and epidemiologic reports bear on the issue.

It has been shown repeatedly that exercise affects glucoregulation directly by increasing insulin receptor density[76,77] and thus increasing insulin sensitivity.[78] The relationship between improved insulin sensitivity and the risk of type II diabetes mellitus is unclear, however.[79] Similarly, glucose clearance has been shown to correlate dramatically with exercise performance,[80] but again there are no data regarding glucose clearance and the risk of type II diabetes developing.

Abnormal glucose tolerance, however, is recognized as an early stage in the progression toward clinically unmistakable diabetes.[81] A demonstration that exercise helps maintain normal glucose tolerance would provide evidence for a preventive effect of physical activity in regard to the development of type II diabetes mellitus. Unfortunately, both cross-sectional and longitudinal studies have produced equivocal results: of 12 such reports, half showed superior glucose tolerance in exercisers; the remaining 6 found no correlation.[82]

Two recent epidemiologic studies of natives of the South Pacific suggest that physical activity may be one of the variables accounting for the fact that the rates of type II diabetes in rural populations are a third those of natives who have become urbanized. Dietary differences do not account for the observed disparity in incidence.[83] The rural rate was still half the urban rate when adjusted for differences in body weight, but only for men; the rates for women were similar for both populations after this adjustment.[84] The authors suggest that the men's greater physical activity during work may afford them this relative protection.

Thus there is no direct evidence of a role for physical activity in preventing type II diabetes mellitus. Glucose tolerance, the most directly related metabolic variable, has not been shown to be affected by exercise. Insulin sensitivity and glucose clearance are altered by regular physical activity, but their relationship to the development of type II diabetes has not been delineated. Epidemiologic data indicate that the con-

cept of a protective effect should not be abandoned, however. Surety rating 0.

Colonic Motility

Because continued bed rest is commonly associated with constipation,[85(pp92-93)] and because diarrhea has been reported as a side effect of long distance running,[86,87] it is tempting to assume that physical activity has a laxative function. If true, this would constitute yet another important benefit of exercise, because constipation is a very common problem in ambulatory[88] and inpatient care. Indeed, in a gastroenterology text of recent vintage (1983), exercise is promoted as part of the treatment regimen for complaints of constipation: "the patient should be urged to get some exercise every day, particularly if he is a desk-bound worker or a housewife [*sic*]."[89(p724)]

Yet virtually no data exist to support or refute this common belief. An article from 1970 that is repeatedly cited (such as by Vena and Garabrant and co-workers[90,91]) indicates a laxative effect of physical activity, but in this study nearly all subjects were inpatients with gastrointestinal tract disease, physical activity was not a controlled independent variable, and there are no quantitative data reported.[92] The only other pertinent study is available in abstract only and shows no consistent change in whole-gut transit time following an increase in physical activity.[93]

More than constipation may be at issue here. Striking epidemiologic studies have recently been published indicating that the incidence of colon cancer is higher in men whose occupations are classified as sedentary ($P < .001$[90] and $P < .0001$[91]). No such relationship was found for any other cancer site, including the rectum. Because no definite effect of physical activity on colonic motility has been documented, however, these results are difficult to interpret. There is a clear need for simple, well-designed tests of gut transit time and physical activity. Surety rating 0.

Exercise Risks

Sudden Death

Until recently it was argued by some that vigorous physical activity, or at least marathon running, might award its participants an immunity to coronary artery disease.[94] In addition, however, to autopsy-proved coronary artery disease in marathoners,[95] there are now at least 75 reported cases of sudden death while jogging or running. Most of these endurance exercisers died of coronary insufficiency.[36]

Sufficient data have now been gathered to permit a quantitative estimate of the increase in cardiac risk during exercise. The death rate for regular joggers in Rhode Island over a five-year period was seven times higher while exercising than while sedentary.[96] A more recent study allows comparison of the increased risk incurred during exercise with the decrease in risk associated with regular physical activity.[97] As shown in Figure 1, the average incidence of cardiac arrest for a habitually vigorous man, which includes his risk while exercising (the transient square wave increase), is still a third the incidence rate for a sedentary man. Moreover, the risk assigned to the sedentary man assumes that he never engages in strenuous physical activity.

It will be most interesting to see if subsequent investigations confirm these dramatic data. Their implications regarding the net cardiac risk and benefit of physical activity are quite clear. Surety rating 2+.

Exercise Addiction

There are anecdotal and case reports that in some persons who take up endurance exercise, a psychophysiologic addiction to it develops. These "addicts" believe they require daily exertion to cope with life; they have withdrawal symptoms, including irritability, depression and anxiety, when external circumstances force abstention, and they have a tendency to continue exercise when it is medically or socially contraindicated.[98]

Only one experimental study has been done to try to elicit these symptoms in regular runners. This experiment involved abstaining from exercise for only 24 hours; results were weakly positive in a small subset of subjects (seven runners).[99]

None of the case reports of addiction involve persons pursuing physical activity in moderation: all are regular endurance exercisers whose workouts total as much as 100 miles per week. Yet precise descriptions of the addictive phenomenon in these cases clearly imply that certain personalities are at risk before they even begin an exercise program.[100,101] Unfortunately, these reports do not agree on particular traits that might be sought to identify such persons. Surety rating 1+.

Musculoskeletal System—Amenorrhea and Bone Loss

The pathogenesis of exercise-associated amenorrhea is not well understood. It appears that high levels of exercise training may interact with a reduction in body fat percentage (resulting at least in part from the exercise training itself) and with other factors such as stress and poor diet, leading to an alteration of the endocrine milieu, a cessation of menstrual cycling and resultant tonically low estrogen concentrations.[102] Alarmingly, exercise-associated amenorrhea has recently been associated with decreased bone mineralization: nonmenstruating exercisers were shown in several studies to have a lower bone density than eumenorrheic controls.[103-107]

Thus, while physical activity may slow or prevent bone demineralization (see the section on Bone Density), too much exercise ironically may lead to increased bone loss. No specific level of exercise training has been associated with the development of amenorrhea. It is sobering, however, that the incidence in competitive athletes may be as high as 50%.[102]

Nevertheless, the general intensity, frequency and duration used in the studies of physical activity for preventing bone loss are well below those of an amenorrheic athlete. It therefore seems reasonable to conclude that, if practiced in moderation, physical activity sufficient to protect against postmenopausal osteoporosis carries little risk of inducing the opposite phenomenon. Surety rating 2+.

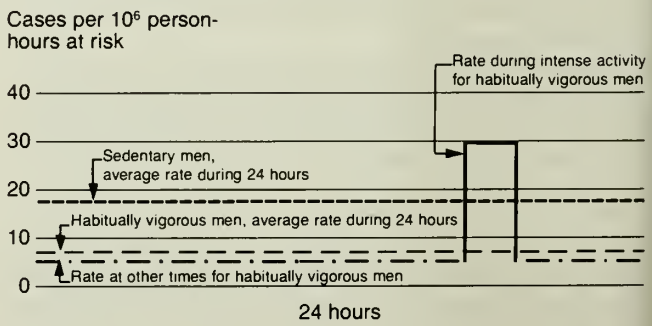

Figure 1.—Risk of primary cardiac arrest during vigorous physical activity and at other times, by level of habitual activity (from Siscovick et al[35]; reprinted by courtesy of *Public Health Reports*).

Musculoskeletal System—Trauma

The risk of bodily injury varies not only with the particular sport involved but also with factors such as climate, equipment and training. Estimating a person's risk is difficult.[108] But some perspective can be gained from the experience with running: for example, among 922 participants in a 10-km road race, a third had a musculoskeletal injury related to running in the following year.[26] The available data, however, clearly indicate that the incidence of injury is directly proportional to exercise intensity, frequency and duration. No data are available to suggest a threshold level of activity beyond which risk climbs steeply; such data would be valuable in selecting a level of activity that optimizes exercise benefits while minimizing risk. Surety rating 2+.

Decreased Libido

There are anecdotal reports of a decrease in libido in some distance runners during intense training. Interestingly, serum testosterone levels were shown in one report to be lower in (male) runners than in controls, but libido was not investigated in parallel.[109] No data on this subject are available for women, though intense exercise clearly affects the female hypothalamo-pituitary-gonadal axis (see Bone Density). Surety rating 0.

Diarrhea

As noted in the discussion of colonic motility, diarrhea has been reported as a common problem in distance runners.[87] There are case reports but no data sufficient to estimate the incidence of this complaint nor the exercise intensity required to produce it. Again, exercise intensity and frequency appear to play a role: in the case reports, episodes of diarrhea were associated with increased or particularly strenuous exertion.[86] Surety rating 1+.

Conclusion

The major findings of this report can be summarized as follows:

- Physical activity has been consistently associated with an increase in self-esteem and a decrease in the risk of hypertension, obesity and postmenopausal osteoporosis. It also appears to have an independent effect in reducing cardiovascular risk.
- Physical activity has not been shown to promote smoking cessation, affect personality or cognition, decrease the risk of diabetes, improve sleep or increase colonic motility.
- For other proposed benefits—improved serum lipid profile and improved affect—there are more supportive than negative data.
- Leisure-time and work-associated activities are not equivalent in their health maintenance effects: the latter has not been shown to promote normotension or to have an independent effect on cardiovascular risk; further, it is positively rather than inversely related to smoking behavior.
- Exercise-associated risks of cardiac arrest, amenorrheic bone loss and musculoskeletal trauma are well documented; the risk of exercise addiction, diarrhea and a decrease in libido have much less support in the literature. With the exception of the risk of cardiac arrest, all these negative consequences of exercise have been shown to be minimized or eliminated by exercising in moderation.

In the current world of competing health care schemes and claims, one of the primary strengths of traditional medicine is its adherence to rigorous scientific standards in evaluating new therapeutic agents. Many of the proposed benefits of exercise do not meet such rigorous standards.

Fortunately there is no need to wait for further research to elevate these claims to legitimacy, as may occur for some of them. Physical activity has already been shown to be an effective agent in health maintenance. Practitioners are urged to make assessment of exercise habits a regular part of the medical history and exercise prescription[110,111] a regular part of their preventive care. Physical activity, however, is not a miracle drug. We would do well not to dilute the elixir with unsubstantiated claims.

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Clinicopathologic Conference

Subacute Leukoencephalopathy Complicating Acute Lymphoblastic Leukemia

Discussants
FRANCIS M. FILLOUX, MD, *and* JEANNETTE J. TOWNSEND, MD

JEANNETTE J. TOWNSEND, MD:* In January 1984, this patient, at the age of 22, was seen because of myalgias, arthralgias and low-grade fevers. A hypereosinophilic syndrome followed resulting in weight loss, lethargy and intermittent apnea, eventually leading to the diagnosis of non-B-, non-T-cell acute lymphoblastic leukemia. Treatment was initiated with COMLA (cyclophosphamide [Cytoxan], vincristine [Oncovin], intravenous [IV] administration of methotrexate with leucovorin calcium "rescue" and cytarabine [cytosine arabinoside]). Although he was lethargic at the time of diagnosis, there was no evidence of central nervous system (CNS) leukemia.

Over the ensuing eight months he received three 11-week cycles of COMLA. Peripheral neuropathy developed, prompting a reduction in the dosage of vincristine. Complete remission was achieved. Two months later (January 1985) a routine cerebrospinal fluid (CSF) examination showed 75 leukocytes, most of which were lymphoblasts. No other site of recurrence was identified. Doxorubicin (Adriamycin) hydrochloride, vincristine and prednisone were instituted along with methotrexate given intrathecally (15 mg twice per week). Despite these measures, lymphoblasts were still found in the CSF. A regimen of 6-mercaptopurine was begun and twice a week methotrexate was administered intrathecally. The meningeal leukemia persisted, but results of a neurologic examination remained normal. A computed tomographic (CT) scan showed mildly increased ventricular size and sulcal widening. In May 1985 an Ommaya reservoir was placed. Two weeks later, *Staphylococcus epidermidis* ventriculitis was diagnosed and was successfully treated with intrathecal and IV administration of vancomycin hydrochloride and rifampin by mouth. Finally in July 1985 (six months after his meningeal leukemia was discovered), examination of a CSF specimen showed no abnormalities. Although on neurologic examination no abnormalities were found, he suffered from nausea, vomiting, fatigue and weight loss. A CT scan of the brain was unchanged.

On August 22, 1985, he was readmitted to hospital after a three-week deterioration in mental state. Initially he had apathy, followed by progressive disorientation, memory dysfunction, somnolence, weakness and stumbling. Episodes of "staring into space" had also occurred. On examination he was quiet and lethargic with a flat affect. He was disoriented to time and to his birth date. Left-right confusion and perseveration were present. A minimal flattening of the right nasolabial fold was present. The remainder of the cranial nerve examination showed no abnormalities. On motor examination he had diffuse mild hypertonia with hyperreflexia, upgoing toes and bilateral ankle clonus. There was mild right iliopsoas weakness, and repetitive fine-motor movements were slowed in both upper extremities. Palmomental, glabellar, grasp and snout reflexes were present. There was no meningismus. The CSF examination showed 1 leukocyte per μl and 3,000 erythrocytes per μl (a traumatic puncture), a protein level of 91 mg per dl and a glucose level of 58 mg per dl (peripheral glucose value was 76 mg per dl). A pronounced increase in the signal intensity from the cerebral white matter was noted bilaterally on spin-echo sequence magnetic resonance imaging scans (Figure 1), and an electroencephalogram (EEG) showed diffuse slow waves.

Two days later generalized status epilepticus developed with right focal features requiring treatment with IV administration of phenytoin and phenobarbital. He remained unresponsive to voice, and the EEG showed prominent left temporal slow waves. A CT scan of the brain was done, revealing a ringlike area of contrast enhancement in the left frontal lobe and possibly in the right frontal lobe with areas of gyral and ependymal enhancement and evidence of midline shift (Figure 2). Repeat CSF analysis showed six leukocytes per μl and no erythrocytes; the CSF protein level had risen to 336 mg per dl, while the CSF glucose value remained normal. An intracranial opportunistic infection was suspected, and multiple antibiotics were administered including amphotericin B, pyrimethamine and sulfadiazine. IV administration of mannitol was also instituted. Despite all these therapeutic measures, his condition deteriorated. He became comatose with decerebrate posturing and asymmetric, unreactive pupils and

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(Filloux FM, Townsend JJ: Subacute leukoencephalopathy complicating acute lymphoblastic leukemia—University of Utah [Clinicopathologic Conference]. West J Med 1987 Feb; 146:207-212)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ALL = acute lymphoblastic leukemia
CNS = central nervous system
COMLA = cyclophosphamide, vincristine (Oncovin), methotrexate, leucovorin calcium and cytarabine
CSF = cerebrospinal fluid
CT = computed tomography
DIC = disseminated intravascular coagulation
EEG = electroencephalogram
IV = intravenous
PML = progressive multifocal leukoencephalopathy

died on September 6, 1985, 15 days after admission to the hospital.

Discussion

FRANCIS M. FILLOUX, MD:* It is an unfortunate consequence of modern medical therapeutics that successful treatment of a life-threatening condition is not uncommonly tempered by the development of diseases that—albeit delayed—may ultimately prove as devastating as the original one. This is especially so with the treatment of refractory forms of malignancy. In reviewing the many neurologic complications of acute leukemia applicable to the case described here, it will become apparent that many are iatrogenic.

This patient survived 1½ years with acute lymphoblastic leukemia (ALL). He died of a subacute encephalopathy characterized by personality change, dementia, apathy, stumbling, seizures and, finally, progressive obtundation and coma. We will begin by briefly reviewing the various neurologic complications of leukemia (see Table 1) and then address specifically the differential diagnosis of subacute encephalopathy in a patient with ALL.

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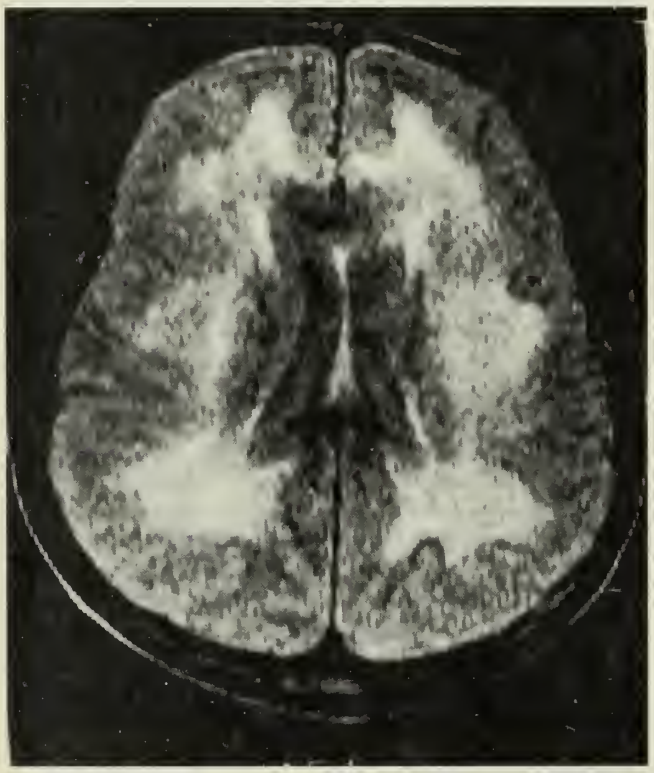

Figure 1.—A T_2 weighted magnetic resonance imaging scan shows bilateral symmetrical increased signal from the cerebral white matter.

Before the advent of successful systemic chemotherapy for childhood leukemia, certain neurologic conditions were prominent in the natural history of the disease. These included primarily leukemic infiltration of the central nervous system, CNS hemorrhage and CNS dysfunction resulting from disseminated intravascular coagulation (DIC).

The initial success in the treatment of ALL was accompanied by a very high rate of CNS relapse (50% to 75% of survivors). It is now apparent that the central nervous system is, in effect, a "sanctuary site" where leukemic cells are protected by the blood-brain barrier from systemically administered chemotherapeutic agents. The introduction of prophy-

TABLE 1.—*Neurologic Complications in Leukemia*

Complications related to leukemia itself
CNS leukemic infiltration
CNS hemorrhage
Disseminated intravascular coagulation
Sinus thrombosis with hemorrhagic infarction
Complications related to both leukemia and its treatment
Opportunistic CNS infection
CNS hemorrhage (thrombocytopenia)
Nonbacterial thrombotic endocarditis
Complications related to the treatment of leukemia
Radiation-induced CNS injury
Methotrexate neurotoxicity
Neurotoxicity from other antineoplastic agents, such as cytarabine, carmustine (BCNU) and the like
Secondary CNS neoplasm
Primary CNS lymphoma

CNS = central nervous system

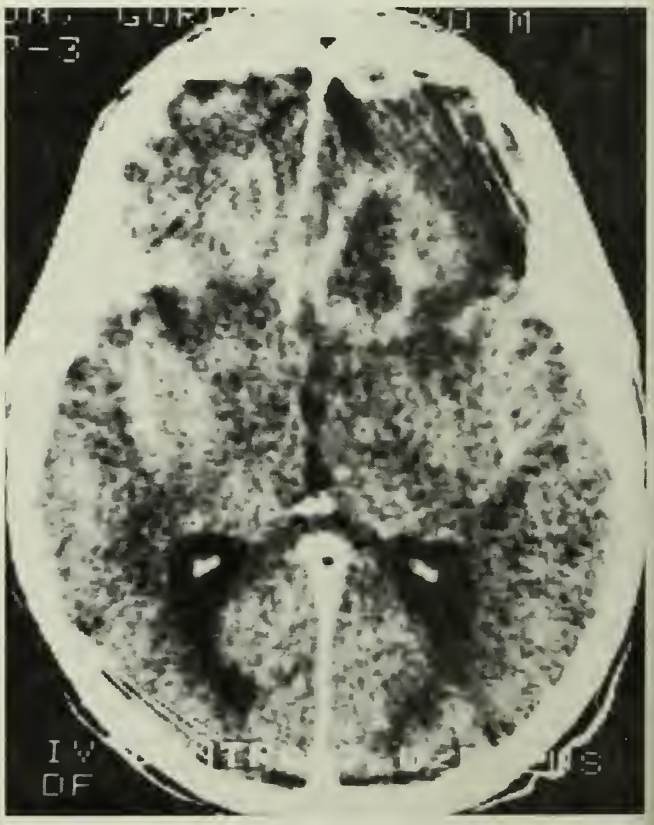

Figure 2.—A contrast-enhanced computed tomographic scan of the cerebrum shows bilateral frontal ringlike enhancing lesions and some gyral enhancement. Evidence of edema surrounding the lesion on the left side was seen at other levels.

lactic craniospinal irradiation with or without intrathecal administration of chemotherapy (primarily methotrexate) has profoundly reduced the incidence of this complication. Nevertheless, as documented by the case described here, CNS leukemia still occurs and must be considered in the differential diagnosis. The clinical features are those of leptomeningitis, often combined with symptoms of increased intracranial pressure. Nausea, vomiting, headache and papilledema are common. There may be cranial nerve dysfunction related to basilar meningeal infiltration, or increased appetite with weight gain presumably related to hypothalamic involvement. Seizures, ataxia or other neurologic signs may also be present, although these are less common. Alternatively, as in this patient, the initial CNS relapse may be asymptomatic, only to be discovered on routine lumbar puncture. The diagnosis is confirmed by lumbar puncture. Although serial CSF analyses may be necessary, leukemic cells will eventually be found and hypoglycorrhachia with mild elevation of the CSF protein level may be present. In rare cases, leukemic masses will be found within brain parenchyma, appearing as hyperdense masses with uniform enhancement on computed tomographic scans.[1,2]

Intrathecal chemotherapy (with or without irradiation) is very effective in preventing the development of CNS leukemic infiltration, but less successful in eliminating the infiltrate once it is present. As in this patient, subsequent CNS relapse is common despite intensive chemotherapy.[1] Nevertheless, CNS leukemic infiltration alone can hardly have accounted for this patient's progressive deterioration.

Hemorrhage, hemorrhagic infarction and dural sinus thrombosis are now rarer complications of acute leukemia, although the latter has recently been associated with a hypercoagulable state induced by the use of L-asparaginase.[3,4] Intracranial hemorrhages most commonly accompany a "blast crisis" in which a peripheral leukocyte count of greater than 100,000 cells per μl is associated with hyperviscosity and subsequent thrombosis. Extensive parenchymal hemorrhage often results, exacerbated by the accompanying consumptive coagulopathy and thrombocytopenia. Such a catastrophic event is far less common now with systemic chemotherapy to prevent the occurrence of high lymphoblast counts.

A less apparent form of DIC may result in an acute encephalopathy with superimposed focal brain involvement.[5] The condition is usually progressive, but a milder, reversible form may exist.[6] In the latter, computed tomography may fail to show any abnormality,[6] whereas in progressive cases hemorrhage, infarction or both are invariably evident.[5,6] Our patient suffered from a condition with a more protracted course than is typical of the encephalopathy associated with DIC. Furthermore, the neurodiagnostic findings were incompatible with this diagnosis.

Far more likely to be implicated as a cause for this patient's neurologic decline were the complications from the aggressive treatment of the leukemia and particularly of CNS relapse. For the sake of clarity, these complications can be grouped into three categories: (1) CNS hemorrhage due to drug-induced thrombocytopenia, (2) opportunistic CNS infection and (3) CNS injury from irradiation or chemotherapeutic agents (or both). Even rarer complications that will not receive further attention here include the development of a secondary CNS neoplasm,[7] primary CNS lymphoma and nonbacterial thrombotic endocarditis.

Of the three categories listed above, the first is easily dismissed from consideration here. It is uncommon with platelet counts above 20,000 per μl and presents as an apoplectic event, not as a progressive encephalopathy. The second category, that of opportunistic infections, deserves closer attention. Such infections are frequent in patients with leukemia[8,9] because the immune response is impaired by the disease itself and by its treatment. Although most of these infections are systemic or pulmonary, CNS involvement may take place in as many as 10% of cases.[8] Any clinical syndrome from acute meningitis to slowly progressive encephalopathy may occur, including, of course, meningoencephalitis, cerebritis, cerebral abscess and the like. The organisms involved are also legion and include the herpes viruses, commensal bacteria such as *S epidermidis;* fungi, particularly *Aspergillus, Cryptococcus* and *Candida,* and the opportunistic parasite, *Toxoplasma gondii.*

It is conceivable that single or multiple cerebral abscesses could have resulted in progressive cognitive impairment with apathy and lethargy, but focal neurologic signs might have been expected earlier in the course. Neuroradiologic procedures should provide valuable assistance in such a situation, although they may have actually led to some confusion in this case. The initial procedure, a magnetic resonance imaging scan (Figure 1), showed diffuse white matter involvement. A few days later, after neurologic deterioration had occurred, a contrast-enhanced CT scan suggested more discrete areas of ringlike contrast enhancement in the left frontal and possibly in the right frontal lobes with areas of gyral and ependymal enhancement (Figure 2). This was interpreted as compatible with multiple abscesses and associated cerebritis. Antimicrobial agents effective against fungi and bacterial pathogens were introduced, unfortunately to no avail.

A number of rarer opportunistic infections are more likely to present as a subacute encephalopathy. These include progressive multifocal leukoencephalopathy (PML), varicella encephalitis and CNS toxoplasmosis. The first of these, PML, is a disease virtually confined to immunosuppressed patients, being most frequently seen in adults with lymphoma or chronic lymphocytic leukemia, but recently becoming apparent as a complication of the acquired immunodeficiency syndrome (AIDS).[10] Although it generally presents with encephalopathy accompanied by focal neurologic signs, it is exceedingly uncommon in patients with acute leukemia.

Varicella-zoster virus encephalitis is seen in immunocompromised patients and in the elderly and generally presents with an altered mental state with or without focal neurologic signs.[11] Typically, however, there is evidence of an ongoing or recently resolved zoster eruption that is frequently disseminated or confined to the first division of the fifth cranial nerve (herpes zoster ophthalmicus). A patient is often febrile, and there is generally a mild CSF pleocytosis.[11] Oligoclonal bands have been noted in the CSF of these patients.[12] In our patient, the requisite skin eruption or history of herpes zoster was absent.

Finally, CNS toxoplasmosis is a protean disorder characteristically seen in patients with compromised immune systems. Recently, *toxoplasma* has been identified as a pathogen in AIDS-associated encephalopathies,[13] and it must be considered in any acute or subacute CNS disturbance in an immunocompromised person. Its presentation may be that of a mass lesion, an acute encephalitis or of a subacute encephalopathy.[14] The CT findings are likewise variable. CSF analysis will frequently elicit a low-grade lymphocytic pleocy-

tosis, with or without mild protein elevation. Serologic confirmation of the diagnosis is often difficult, requiring demonstration of a rising or very high serum titer—such as by the Sabin-Feldman dye test—or of an elevated immunoglobulin M anti-*Toxoplasma* titer.[14,15] Biopsy may occasionally be necessary (and warranted) in view of the possible response to antimicrobial treatment. Efforts were made to rule out CNS toxoplasmosis in this patient, and he was empirically placed on a regimen of pyrimethamine and sulfadiazine. His rapid deterioration despite treatment certainly does not exclude the diagnosis.

The last category of disease that must be considered in this patient is that of CNS injury from radiation therapy, chemotherapeutic agents or both. As the treatment of malignancy has become more sophisticated, the breadth of this topic has burgeoned. Extensive reviews are available,[16] hence only a summary is offered here. For simplicity's sake, toxicity from CNS irradiation can be grouped into three temporally defined types: acute, subacute and delayed. The first two are transient and self-resolving, occurring early in treatment or several weeks to a few months later, respectively. Both consist primarily of mild, self-limited headache, lethargy, irritability, anorexia, nausea and vomiting. Delayed radiation toxicity is much different. It occurs six months to several years after completion of CNS irradiation, most commonly following dosages in excess of 2,400 rads, whole brain irradiation.[17] The condition typically presents abruptly as a mass lesion or cerebral infarct, but may follow a more insidious course. On pathologic examination, there is coagulative necrosis, with preferential involvement of white matter. Edema and demyelination may be present, and vascular involvement with fibrinoid degeneration is prominent.[17] The condition is often fatal and no specific treatment is available. It is becoming increasingly apparent that less severe forms of delayed radiation neurotoxicity exist. These include subtle neuropsychological deficiencies, behavioral changes and possibly a subclinical mineralizing microangiopathy with dystrophic calcification.[18] The interrelationships among these various manifestations of delayed radiation-induced neurotoxicity are unclear.

Methotrexate—the chemotherapeutic agent most commonly resulting in significant CNS toxic reaction—can produce three temporally distinct types of complications: acute, subacute and delayed. Again, the first two are generally self-limited. The first takes the form of acute arachnoiditis with headache, nausea, vomiting, meningismus and dizziness as the characteristic symptoms.[16] It occurs in the first few days of intrathecal administration of methotrexate and is associated with a granulocytic pleocytosis and mild elevation of the CSF protein.[16] The condition is most likely due to toxicity from the drug itself rather than its diluent, because it occurs with preservative-free administration and in a dose-dependent manner. The second, or "subacute" form, of methotrexate CNS toxicity is more variable, but generally occurs days to weeks after initiation of chemotherapy. Its presentation may be that of a moderate to severe myelopathy[19] or encephalopathy.[16,20] Recovery is the rule if the dosage of methotrexate or the frequency of its intrathecal administration (or both) are reduced. The pathogenesis of this form of methotrexate toxicity is uncertain. It is seen most commonly with frequent intrathecal administrations of the drug (more than two to three times a week)[16] or with high doses given IV with leucovorin "rescue" (as in the treatment of soft tissue sarcomas in children).[21] (In the latter setting, tumor embolization of the CNS has been postulated as the cause of the transient neurologic disturbance.[20])

Most applicable to the case in question is the delayed form of methotrexate neurotoxicity, also known as disseminated necrotizing leukoencephalopathy.[22] This condition is primarily seen in children treated for acute leukemia with both CNS irradiation and IV administration of methotrexate, with or without intrathecal administration. The condition generally develops months to years after initiating these treatments.[22-25] The clinical picture is remarkably uniform, beginning with behavioral changes, listlessness, emotional lability and social withdrawal, progressing over a period of days to weeks to a mute, akinetic state with gait instability due to pyramidal and cerebellar dysfunction.[26] In general, inexorable deterioration results in death within weeks of onset.

Pathologic changes consist of widespread bilateral white matter destruction with perivascular demyelination and noninflammatory necrotic foci; also typical are axonal swellings or spheroids and surrounding reactive astrocytosis.[22,24,25] The presence of vascular changes, such as hyalinization or fibrinoid degeneration of small vessel walls is variable.[22,24,25] In view of these findings, it is not surprising that CSF examination should generally show a mild elevation of the CSF protein level without pleocytosis. Computed tomography will typically show diffuse, bilateral white matter hypodensity in the centrum semiovale and periventricular regions, often accompanied by variable, irregular contrast enhancement.[2,27] In some cases, however, a more focal process is evident with contrast enhancement that mimics a tumor mass.[28] Magnetic resonance imaging promises to provide an even more accurate diagnostic tool for the identification of this disorder. With spin-echo sequences (T_2-weighted images), bilateral increased signal intensity is seen in the periventricular white matter with some asymmetry.[29]

The pathogenesis of this complication is a matter of great controversy. Most children in whom this condition develops have received both cranial irradiation and methotrexate (generally intravenously and intrathecally)[22-25]; similar pathologic findings, however, have been encountered following either treatment alone.[30] Although several investigators have postulated that the CNS damage results from diluents or preservatives rather than from the drug itself, there is compelling evidence that methotrexate is the primary offending agent.[16] The presence of meningeal leukemia clearly increases the risk of this complication developing, most probably because of impaired methotrexate clearance from the CSF.[16,31,32] Furthermore, there appears to be a correlation between the cumulative dose of methotrexate (given IV or intrathecally or both) and the appearance of delayed neurotoxicity.[16,24] It is possible that radiation toxicity alters the permeability characteristics of the blood-brain barrier, thereby enhancing potential toxicity from parenteral administration of methotrexate.[16]

Other chemotherapeutic agents have been implicated as central nervous system toxins, including carmustine (BCNU)[33] and cytarabine,[34] but these are not relevant to the case at hand.

This patient suffered many of the complications that are associated with the development of disseminated necrotizing leukoencephalopathy. CNS leukemia developed that proved refractory to treatment. He received methotrexate intrathecally frequently over a prolonged period in conjunction with cranial irradiation. Ultimately a progressive encephalopathy

developed, and the findings of the CSF studies and magnetic resonance imaging scan were compatible with this diagnosis. Several ring-enhancing lesions on CT scan led to unexpected diagnostic confusion. Although opportunistic infections were considered, the clinical features and laboratory data in this patient were more typical of severe delayed methotrexate and radiation leukoencephalopathy.

Pathology

Dr Townsend: There was no evidence of persistent leukemia in the systemic tissues. The significant systemic findings included acute tracheobronchitis, focal pulmonary consolidation and multifocal cardiac fibrosis consistent with a healed cardiomyopathy.

The brain weighed 1,585 grams in the fresh state and showed cerebral swelling with bilateral uncal herniation. The brain was sectioned in the CT plane, and bilateral granular hemorrhagic lesions were found in the white matter of the frontal lobes (Figure 3). These lesions measured approximately 3 by 3.5 by 2 cm in greatest dimensions. The white matter surrounding the lesions was yellowish and softened. Although the frontal lobe lesions were confined mainly to the white matter, scattered focal, softened, hemorrhagic lesions were found in the thalamus, globus pallidus and caudate nuclei. The cerebellum and brain stem did not appear abnormal on gross inspection.

On microscopic examination there was extensive disease well beyond the grossly visible lesions. The hemorrhagic granular lesions in the frontal lobes showed widespread fibrinoid necrosis of vessels with petechial hemorrhages (Figure 4). The tissue was necrotic and contained reactive macrophages and astrocytes. Areas adjacent to the visible lesions in the frontal lobe white matter were pale and eosinophilic. Special stains for myelin and axons showed a partial loss of these structures. The white matter was diffusely gliotic. The basal ganglia were gliotic bilaterally and contained the focal necrotic lesions identified grossly. The internal capsule and other white matter tracts contained focal accumulations of swollen axons with calcification (Figure 5).

These findings are diagnostic for severe necrotizing leukoencephalopathy due to methotrexate and radiation treatment.[22,24,25] As mentioned by Dr Filloux, these findings can be seen in patients receiving either methotrexate or irradiation alone or in combination.

Sections from the medial temporal lobe, midbrain and pons showed pallor of the background parenchyma and eosinophilic shrunken neurons. The areas involved were adjacent

Figure 3.—This horizontal section of brain shows bilateral hemorrhagic lesions in the frontal lobe and focal softenings in the basal ganglia.

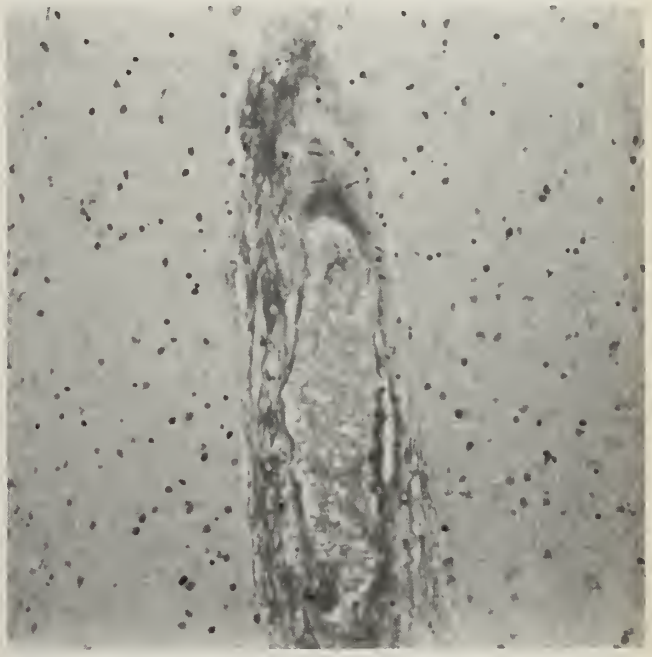

Figure 4.—Fibrinoid degeneration can be seen in this white matter vessel (hematoxylin and eosin stain, × 150).

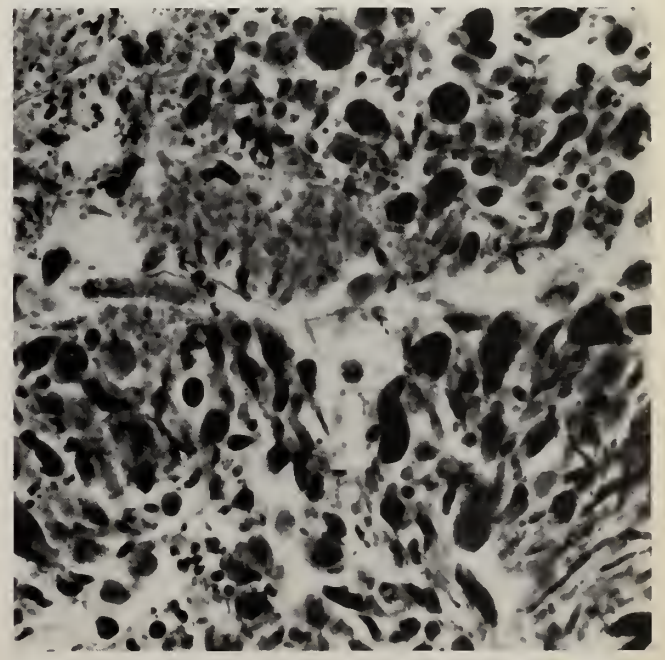

Figure 5.—The silver stain shows swollen axons in the internal capsule (Bodian stain, × 450).

to the subarachnoid space and were more acute than the previously described lesions. These changes have been described in young children treated with methotrexate and have been thought to be caused by direct toxicity of methotrexate bathing the tissue adjacent to the basilar cisterns.[35,36]

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Medical Staff Conference

Issues in Latino Health Care

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Persons of Latino background are making up an increasing percentage of Americans in many areas of the United States. In this timely review, Eliseo Pérez-Stable, MD, Assistant Professor of Medicine at the University of California, San Francisco (UCSF), School of Medicine, illuminates cultural issues that can have an important effect on the physician-patient relationship and on the institution of broader health care programs for Latinos. Dr Pérez-Stable was born in Cuba and immigrated to this country in 1960. He has BS and MD degrees from the University of Miami and received his training in primary care internal medicine at UCSF. He was the recipient of the Henry J. Kaiser Foundation Fellowship in General Internal Medicine and joined the faculty at UCSF in 1981. Besides his role as an excellent clinician and teacher, Dr Pérez-Stable is Director of the Primary Care Internal Medicine Residency Program at UCSF and is supported by two grants from the National Institutes of Health to study and develop effective programs on smoking cessation intervention in Hispanics and the treatment of mild hypertension.*

ELISEO PÉREZ-STABLE, MD:† In this Medical Staff Conference I will present an overall picture of Latino health care issues from a multidisciplinary perspective. First, I will review the demographic profile of Latinos in the United States. Next I will summarize pertinent health care access issues and focus on three specific topics—cardiovascular risk factors, tuberculosis and depression. Finally, I will discuss the concept of cultural barriers to medical care from a Latino perspective.

The cultural and historical roots of Latinos are found in the Iberian Peninsula, in the highly developed indigenous societies of pre-Columbian America and in western and southern Africa. Spain was the dominant colonial power in Latin America, and thus the designation "Hispanics" as a label for Latinos in the United States is not fully acceptable. Hispanic is the official name used by the federal government, but use of this term implies a heritage restricted to Spain. Latino is Spanish for Latin, but it is the prefix attached to the American continent south of the Rio Grande (*Latino* America). Thus, the name Latino reflects the integration of Spanish, indigenous and African cultures that are part of our identity. I prefer to use Latino as a generic label as, for example, does the American Public Health Association. The use of names such as "Chicano" or "Raza" reflects the emergence of ethnic pride among second-generation Mexican-Americans, and these may not be acceptable to recent immigrants or to persons from other subgroups. Other terms such as Spanish or Latin should not be used.

Latinos come from many different countries and each one has a distinct national culture. Whenever possible, the country of origin should be identified and the proper name used in referring to patients, such as Mexican, Salvadorean and so forth. In the United States Latinos share a common language and cultural heritage and, in general, these similarities predominate over national differences.

Demographic Profile

The United States has the sixth largest "Hispanic" population in the world, exceeded only by Mexico, Spain, Colombia, Argentina and Peru. According to the official US census, between 1970 and 1980 there was a 61% increase in the Latino population in the United States from 9.1 to 14.6 million persons.[1] Including estimates of uncounted, undocumented persons and adjusting for growth since 1980, there are probably more than 20 million Latinos, or 8% of the total population in the United States.[2] Demographic projections buttress the contention that Latinos may become the largest minority group in the United States by the year 2000.

Latinos of Mexican origin are the largest subgroup with 59.8% of the total, followed by Puerto Ricans (13.8%) and Cubans (5.5%).[1] The category of "other Hispanics" comprised 20.9% of US Latinos in 1980, and this may now actually be greater as a result of the recent influx of immigrants from Central America. Most Latinos live in urban areas (87%), and 82.9% are concentrated in eight states, with California and Texas containing 51.6% of the total. In 1980 nearly a third of Latinos were foreign-born and approximately a quarter spoke little or no English.[1]

In California 20% of the population is Latino and most are of Mexican origin. Los Angeles and San Jose have the largest proportion of Latinos, who make up nearly 30% of their populations. In San Francisco, Latinos of the "other Hispanic" category outnumber those of Mexican origin.[3]

Health Care Access and Health Care Status

National data from the Health Interview Surveys (HIS) conducted by the National Center for Health Statistics be-

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(Pérez-Stable EJ: Issues in Latino health care—Medical Staff Conference, University of California, San Francisco. West J Med 1987 Feb; 146: 213-218)

Supported in part by Public Health Service grant No. R18 CA39260-02 awarded by the National Cancer Institute, US Department of Health and Human Services.

ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
HHANES = Hispanic Health and Nutrition Examination Survey
HIS = Health Interview Surveys
UCSF = University of California, San Francisco

tween 1978 and 1980 have been analyzed for persons self-identified as Latinos. In general, Latinos made physician visits as frequently as did Anglos (whites not of Latino origin) or blacks, but subgroup differences were present. Mexican-Americans average 4.3 physician visits per person per year, which is significantly lower than the average for Anglos (4.8), blacks (4.8) or other Latinos (5.1 to 6.1).[4] In addition, only a third of Latinos, compared with half of Anglos, made at least one annual visit to a dentist.

Latinos are less likely than any other ethnic group to have any form of medical insurance. A national phone survey by the Robert Wood Johnson Foundation found that 18% of Latino adults lack any insurance or were refused care for financial reasons, which compares with 8.5% of Anglos and 13.4% of blacks.[5] The HIS data show that Puerto Ricans and Cuban-Americans are twice as likely and Mexican-Americans three times as likely as Anglos to be without health insurance.[4] Another survey that included an adequate sample of Latinos in the southwestern states reported that a third lacked any form of medical insurance, compared with 11% of the general population.[6]

These studies indicate that access to health care is not as readily available to Mexican-Americans as it is for the general population. Access does not appear to be a problem among Puerto Ricans and Cubans. Significant economic barriers to adequate health care persist for Latinos, however, especially among the undocumented. Despite the differences in access and health insurance coverage, regional data indicate that Latinos may have a lower age-adjusted mortality rate for the three leading causes of death in the United States.[7] National mortality rates for Latinos, however, are not yet available, and further evaluation of existing data sources is necessary before generalizations can be made.

Even though Latinos may have a lower mortality rate than the general population, the epidemiology of homicide in Los Angeles County reveals a worrisome trend. Death by homicide is 2.3 times more likely in Latinos than in Anglos, and there was a 166% increase in Latino homicides between 1970 and 1979.[8] Alcohol was present in 57% of all tested Latino victims compared with 48% of blacks and 35% of Anglos. These findings may reflect an important social problem that has escaped the attention of the Latino community.

Cardiovascular Risk Factors

Hypertension

An elevated arterial pressure is a major cardiovascular risk factor that may be related to several life-style factors including social and environmental stress. Latinos in the United States have a socioeconomic status that is intermediate between Anglos and blacks, but, in addition, Latinos confront the stress inherent in migration and heightened by the language barrier. Although there is little known about dietary salt intake in Latinos, obesity is more prevalent than in Anglos. Thus it is reasonable to hypothesize that Latinos will have a greater prevalence of hypertension than Anglo-Americans.

The Laredo Project in Texas reported on the prevalence of cardiovascular risk factors in a population-based sample of 389 Mexican-Americans.[9] The prevalence of an elevated diastolic blood pressure (95 mm of mercury or higher) was found at a rate between that reported for Anglos and blacks in the Hypertension Detection and Follow-Up Program. The statewide California survey, however, which included 1,764 Latinos, showed that a diastolic blood pressure of 90 mm of mercury or higher or a systolic blood pressure of 140 mm of mercury or higher was present in 21.5% of Latinos.[10] This rate was not significantly different from Anglos (23.4%) or Asians (20%) and lower than the prevalence found in blacks (35.2%).[10] More recently, a report from the San Antonio Heart Study found an overall age-adjusted prevalence of hypertension for Mexican-Americans that was similar to or lower than that for Anglos of the same socioeconomic status.[11]

Surveys of hypertension in other Latino subgroups have been limited to children and adolescents. In Dade County (Miami), a hypertension screening program among 24,536 junior high school students between 1979 and 1981 reported that male Cuban adolescents had a higher prevalence of elevated blood pressure than did both Anglos and blacks.[12] No significant differences were observed among female adolescents. In New York, the "Know Your Body Study" reported a significantly higher blood pressure in 346 Puerto Rican children than in a comparison group of Anglo children.[13]

The Hispanic Health and Nutrition Examination Survey (HHANES) conducted between 1982 and 1984 was a comprehensive evaluation of the health status of more than 9,000 Latinos representative of the three major subgroups. Results from the Mexican-American sample have been analyzed, showing a lower prevalence of hypertension (16.8% for men, 14.2% for women) than in other national surveys of Anglos and blacks.[14] Comparisons among the three subgroups will be possible in the near future. If true subgroup differences exist, the greater African influence in Puerto Rico and Cuba may partly account for this.

In summary, current studies indicate that the prevalence of hypertension in Latinos may actually be lower than in other ethnic groups. Mexican-Americans, however, lag behind Anglos of similar socioeconomic status in their level of treatment and degree of control.[11] Preliminary results from HHANES show that 53.9% of Mexican-Americans are aware, 39.8% receive treatment and 19.4% are adequately controlled.[14] This compares somewhat unfavorably with other Americans who average 65% to 90% awareness, 50% to 75% under treatment and 30% to 50% in control (Table 1).[10,11,15]

TABLE 1.—*Summary of Cardiovascular Risk Factors in Latinos*

Risk Factor	*Comparison With General US Population*
Hypertension	Lower overall prevalence in adults; less awareness, treatment, control
Cigarette smoking	More men smoke, fewer women smoke
Lipids	Higher triglycerides, lower HDL cholesterol levels, total cholesterol similar
Diabetes mellitus	Non-insulin-dependent type is three times more likely in Mexican-Americans
Obesity	Greater overall prevalence, women more likely than men

HDL=high-density lipoprotein

Cigarette Smoking

Regional and national surveys of smoking behavior in Latinos have until recently reported a lower prevalence of current smokers when compared with other Americans. Evaluation of sex differences in Latino smoking behavior shows that the rate for women is consistently lower than that for Anglo and black women.[16] The smoking rate for Latino men, however, is now higher than for Anglo men and comparable to the rate for black men.[16] Marcus and Crane examined the 1979-1980 Health Interview Survey Latino sample[16] and found no variation in the male-female differences in smoking behavior by country of origin. The HHANES results show that 43% of Mexican-American men currently smoke cigarettes,[17] compared with 38% of Anglos and 45% of blacks in the 1980 HIS. Conversely, Mexican-American women reported a 24% prevalence of smoking in the HHANES study, less than the 30% for Anglo and black women in recent surveys. An increasing level of acculturation was associated with cigarette smoking among Latino women but not among men.

Although their proportion of smokers may be increasing, Latinos have consistently reported smoking fewer cigarettes per day than Anglos or Blacks.[16] For example, 41% of smoking Mexican-American men report smoking less than ten cigarettes per day, which compares with 9.6% of Anglo and 17.5% of black men.[17] If this self-reported behavior is confirmed by biochemical measures, and Latinos are in fact light smokers, then community-based cessation programs may have a greater chance for success.

Obesity

Obesity, defined as 120% or greater of "desirable weight," is more prevalent among Latinos of Mexican background. Population-based studies in Texas and California have reported that about 45% of Mexican-American women are overweight compared with 29% of Anglo and 35% of black women.[18,19] Latino men also have a greater average weight than Anglo men, but the differences are less striking. Although dietary and other life-style habits contribute to the greater prevalence of obesity in Latinos, there are additional cultural factors involved. In a survey from Texas, Latinos of both sexes tend to agree with the statement that "Americans are too concerned about weight loss," implying that the Anglo cultural ideal of "leanness" has not been fully accepted by Latinos.[20]

Lipids

Data from the San Antonio Heart Study have shown that Mexican-Americans in Texas carry a profile of "obesity related" cardiovascular risk factors.[21] These risk factors include a higher prevalence of obesity, glucose intolerance and lipid profile abnormalities. Elevated serum triglycerides and lower high-density-lipoprotein (HDL)-cholesterol levels are noted at a younger age in Texas Latinos than in comparable groups of Anglos.[21] Total serum cholesterol levels, however, have not been found to differ significantly from those in Anglos in regional studies.[21] The HHANES results indicate that nearly 29% of Mexican-American adults have moderate to high risk levels of serum cholesterol (greater than 240 mg per dl), which is similar to the proportion found in the general US population.[22]

Changes in dietary habits as a result of acculturation and a rising socioeconomic status may alter these risk factors. Mexican-American women living in the San Antonio suburbs have significantly lower levels of serum triglyceride and higher levels of HDL cholesterol when compared with age-matched women living in a barrio.[21] In contrast, Mexican-American men have increases in the total and low-density-lipoprotein-cholesterol levels with rising socioeconomic status.[21]

Diabetes Mellitus

The most important difference in cardiovascular risk factors between Mexican-Americans and Anglos is the prevalence of impaired glucose tolerance. Non-insulin-dependent diabetes mellitus is three times more prevalent among Mexican-Americans than among Anglos. The initial report from the Laredo Project indicated that Mexican-American men and women have a 10% to 11% prevalence of fasting hyperglycemia (greater than 140 mg per dl) compared with 4% for Anglo subjects in HANES I.[19] The San Antonio Heart Study has substantiated these data by using glucose tolerance tests and standard diagnostic criteria developed by the National Diabetes Data Group.[21] A rising socioeconomic status in Mexican-Americans from the barrio sample to the suburbs sample is paralleled by a decreasing prevalence of diabetes to the point that differences from the Anglo population disappear.[21]

Additional evidence that diabetes is a major health problem in Mexican-Americans comes from evaluating its major complications. In the state of Texas there is a sixfold increased risk of end-stage renal disease due to diabetic nephropathy among Mexican-Americans compared with Anglos and blacks.[23] The risk of any retinopathy was found to be three times more common in Mexican-Americans when compared with Anglos in a sample of patients with diabetes from the San Antonio Heart Study.[24] Diabetes may not only be more prevalent in Mexican-Americans, but it may also manifest more severe complications.

The higher prevalence of obesity among Mexican-Americans does not fully explain the greater risk of diabetes. Stern and colleagues stratified a population-based sample according to body weight and found a higher prevalence of diabetes among Mexican-Americans for each weight and sex category when compared with Anglo-Americans.[25] One possible explanation may be the genetic influence of the indigenous American peoples reflected in Mexicans but not in Anglos or blacks.[26] Comparison studies with other Latino subgroups in the United States will help address this question.

Tuberculosis

Immigrants from countries with a high prevalence of tuberculosis are expected to have an increased risk of entering the United States with active disease or of tuberculosis developing while they are residing here. Officially reported case rates from Latino America generally underestimate the true prevalence of tuberculosis by a factor of two to five. Control of tuberculosis comparable to that in the United States (1984 case rate = 9.4/100,000), however, has been achieved in both Cuba (1982 case rate = 8.3/100,000)[27] and Puerto Rico (1984 case rate = 12.8/100,000).[28] Mexico and the Central American countries have case rates of tuberculosis that are between 35 and 90 per 100,000 population.[29] These are four to ten times greater than the 1984 case rate for the US population.[28] The fact that so many Latino immigrants from Mexico and Central America enter the United States without docu-

ments means that there is no systematic screening program for tuberculosis. Thus the potential exists for tuberculosis to become a major health problem among Latinos in the United States.

The case rate of tuberculosis in US Latinos is estimated at 16.2/100,000 population for 1984.[28] This translates to an overall relative risk of 1.7 in comparison to the general population, but tuberculosis may be of special importance in Latino children. In 1984, of all reported cases of tuberculosis in persons younger than 5 years of age, 26.5% occurred in Latinos.[28] A review of 330 pediatric charts at a community health center in San Francisco between 1978 and 1983 found a 30% prevalence of positive tuberculin tests, an 11% overall rate of tuberculin conversions and five cases of active tuberculosis.[30] The conversion of tuberculin tests from negative to positive in US Latino-born children may indicate the presence of unsuspected transmission of tuberculosis.

A community-based survey of 1,879 Mexican, Central American and US-born Latinos was conducted by the San Francisco Division of Tuberculosis Control in 1983-1984. The overall rate of positive tests was 37%, with birthplace outside of this country and age the most important predictors of tuberculin reactivity (Figure 1).[31] Even among US-born Latino children younger than 5 years of age, rates of positive tests were 2%, exceeding the recommended threshold for routine screening of population groups.[32] Neither history of vaccination with the bacillus Calmette-Guérin or duration of time residing in the US among the foreign-born influenced the rate of positive tests. Based on these data, tuberculosis screening and prevention activities should be a priority in meeting the health care needs of Latino immigrants from Mexico and Central America.

Although the magnitude of the tuberculosis problem does not approach that found among Asian immigrants, Latinos also have a higher prevalence of primary drug resistance. Culture results reported to the Centers for Disease Control show an 11.8% prevalence of drug-resistant tuberculosis among Latinos in comparison to 4.9% for Anglos, 6.1% for blacks and 14.8% for Asians.[33] Clinically, this implies that the initiation of antituberculosis therapy in Latinos should include two drugs in addition to isoniazid.

Depression

The most significant health problems in Latino immigrants lie in the area of mental health. Immigrants entering the United States confront a major adaptation process that manifests in many different ways, especially depression and other symptoms of the posttraumatic stress syndrome.

Depressive symptoms measured by self-report scales have been found to be significantly greater among Mexican-Americans than in Anglos or blacks. The Alameda County (California) study reported the following proportions of respondents scoring above the cut-off for significant symptoms: 14.6% for Anglos, 18.1% for blacks and 28.9% for Latinos.[34] A phone survey in Santa Clara County (California) found similar levels of depressive symptoms in Anglos and English-speaking Latinos, but significantly higher levels of depressive symptoms in Spanish-speaking Latinos.[35] These data suggest that the relative lack of societal integration resulting from low acculturation may account for increased depressive symptoms among Latinos.

The prevalence of lifetime clinical depression among Latinos in the HHANES study was comparable to published rates of lifetime depression in other epidemiologic studies of Anglos or blacks.[36] A self-selected sample of medical outpatients at the UCSF-affiliated clinics showed that the prevalence of lifelong major depression was not significantly different in Spanish-speaking patients (25% of 55) from that in English-speaking patients (18% of 237). Although these data indicate that the relative frequency of clinical depression in Latinos is similar to that of the general population, definite conclusions are premature at this time. Latinos, however, are more likely to present to a primary care physician with somatic complaints when depressed, and, in general, they feel more stigma from using mental health services.

Over the past eight years a large number of Central American immigrants have entered the United States fleeing circumstances of war, economic hardship and outright political persecution. In El Salvador, for example, 20% of the country's population has been displaced either in exile or in existing refugee camps. Immigrants who make it to the United States show a spectrum of mental health problems similar to that observed among US soldiers returning from the Vietnam war. Manifestations of the posttraumatic stress syndrome have resulted in increased episodes of clinical depression, substance abuse, antisocial behavior, family violence and somatization disorder.[37] Awareness of the circumstances that affect these patients and maximum use of available community resources are the initial steps in managing this problem.

Cultural Barriers to Health Care

Language

The language barrier that exists between Spanish-speaking Latinos and English-speaking health care providers presents an obvious impediment to quality health care services. The Robert Wood Johnson Foundation phone survey[5] found that 17% of Latino respondents with emergency room visits in the previous year had been "not at all satisfied with most recent visit" compared with 11% of Anglos and 7% of blacks. In California, the proportion of Latino physicians in 1980 was only 1.7%.[38] Given the plateau in medical school minority admissions in the past decade, it is unlikely the number of Latino physicians will increase significantly in the next 25 years. Thus, the language barrier will be an issue for many physicians who practice in the southwestern states.[39]

The need for a translator during patient visits changes the

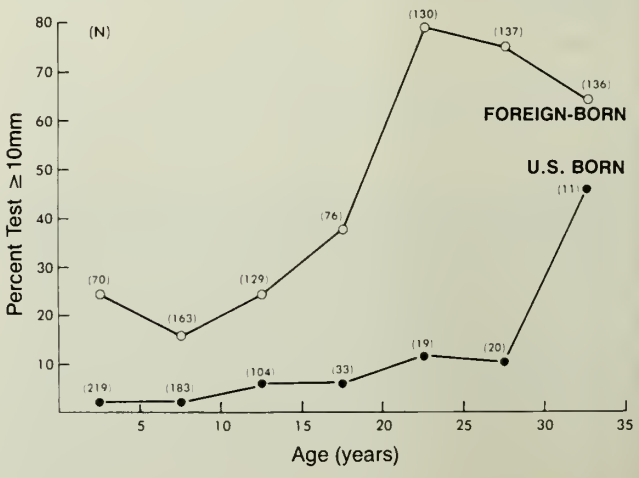

Figure 1.—Proportion of Latinos with positive tuberculin tests by age and birthplace.

nature of the patient-physician interaction. The translator is a third active person creating a triangular interaction. By setting up the physical space in an equilateral way, physicians can maintain direct eye contact with their patients (Figure 2). Translators often act as cultural interpreters and may assist (or hinder) communication with a patient in other ways. Physicians should request a translation of all patient-translator interactions because important details may be omitted in the abbreviated response to a question. Similarly, a translator may respond to a question before the patient has spoken; thus one should request translations of all questions asked of the patient.

Family members are often the only available persons to translate, but frequently they are the least desirable. Adolescents or children are inappropriate translators for adult patients because of the intimate details of the medical history. Adult children of elderly persons may heighten the language barrier by being overprotective and responding directly to questions because they "already know the answers." Trained translators hired by hospitals and clinics with a significant number of non-English-speaking patients may greatly facilitate patient-provider communication and improve the quality of care delivered to this population.

'Familismo'

Latinos tend to have a collective loyalty to the extended family that ranks higher than individual needs. This may be manipulated by the health care provider in an effort to initiate a life-style change or in guaranteeing compliance with a medical regimen. For example, an adult cigarette smoker may find motivation in quitting for his or her children's sake if not for personal health reasons. Similarly, the intact structure of an extended family can provide a buffer system at times of emotional stress. There are also members of the extended family *(compadres* or *comadres)* who usually have no blood relationship, but they are still considered "family."[40]

The family structure in Latinos may also at times hinder appropriate health care delivery. Showing illness or weakness to outsiders—that is physicians—may be a shameful or painful experience. The existence of a male-dominated family hierarchy may increase cultural barriers between Latino patients and non-Latino health care providers. Recognizing and respecting this hierarchy, however, is important, especially when dealing with older patients. Machismo exists to a greater or lesser extent in most Latino men but it may not always carry a negative connotation. The role of protector,

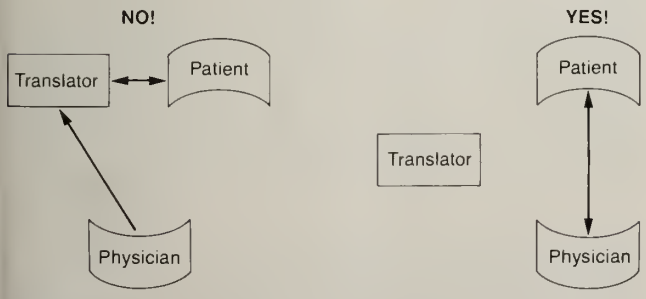

Figure 2.—The diagram depicts the patient-translator-physician triangle. When sitting in an office, do not position the translator next to the patient, but position the translator equidistant from both of you. Whenever asking a question through a translator, engage face-to-face with the patient so that he or she will understand the nonverbals. Whenever a patient answers a question through the translator, ask him or her to address you.

strong and in control, is perceived as a positive aspect of machismo and thus expected behavior in Latino men. Women continue to have the dominant role of caretaker and to provide the principal source of health information to the family. Awareness of these cultural scripts may help physicians in their management of Latino patients.

Cultural Expectations of 'El Doctor'

Latino patients view physicians as important authority figures with rank on the level of priests. Although expecting an authoritative expert, Latinos also want a friend they can talk to in their physician. In Spanish, this is best described by the term *personalismo,* which can be loosely translated as "formal friendliness." The impersonal characteristics that frequently accompany modern American medicine are not acceptable in Latino culture. Physicians may be evaluated on the basis of their verbal communication skills rather than their medical knowledge.

In Latino America, the powerful are legitimate to the extent that they respect the *dignidad* ("worthiness") of ordinary citizens. Patients will often establish relationships with physicians based on paternalistic dependence, but these will disintegrate if a tone of *respeto* ("respect") is not maintained. Quesada has traced this relationship to the patron-peon dynamics of prerevolutionary Mexico, and he has called it the dependency-*dignidad* paradox.[41] For example, Latino patients expect a handshake in greeting, and not offering this is considered rude. As patients get to know their physician, some form of physical contact other than the examination is culturally accepted behavior. The polite form of "you" in Spanish *(usted)* should always be used with patients because the informal form *(tu)* is considered impolite and inappropriate to the patient-doctor relationship.

The concept of *personalismo* reflects a general cultural script for Latinos labeled *simpatia* by a group of social psychologists. Triandis and co-workers[42] found that Latinos are more likely than Anglos to expect a high frequency of positive social behavior and a low frequency of negative social behaviors. For example, patient-physician interactions characterized as neutral by Anglo patients may be perceived as negative by Latino patients. Thus, the inattention among non-Latinos to the presence of the *simpatia* script when interacting with Latinos may lead to misunderstandings.

Cultural Reactions of Latino Patients

Latinos tend to express emotions more openly when confronted with a crisis such as illness. In this setting, remaining "calm" is culturally inappropriate and an emotional discharge is expected behavior. Latino women in particular have been characterized as having a lower pain threshold and complaining more frequently and vehemently than persons of other ethnic groups, but there are no data to support this. The higher rate of prescribed psychotropic medications in Latinos may reflect this misconception.

Finally, the process of death and dying in Latinos may elicit different reactions. The standard practice of informing a person of a terminal diagnosis may not always be appropriate. Denial is an effective defense mechanism and should be considered in the Latino cultural context. This is especially the case for older Latinos for whom only palliative therapy can be offered.

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Epitomes
Important Advances in Clinical Medicine

Otolaryngology/Head and Neck Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology/head and neck surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in otolaryngology/head and neck surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology/Head and Neck Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Anosmia—Evaluation and Treatment

As many as 2 million Americans have lost their sense of smell. Many of these patients have sought advice from primary care physicians and specialists, never receiving satisfying explanations. Over the past two years, the Nasal Dysfunction Clinic at the University of California San Diego Medical Center has had the opportunity to fully evaluate 63 patients. The evaluation included an age-adjusted olfactory threshold and odor identification test, rhinomanometry, nasal cytology, nasal endoscopy, computed tomographic (CT) scan and a trial of medical treatment. In all, 33% (21) of the patients had anosmia or hyposmia due to inflammatory nasal disorders, 32% (20) due to postviral olfactory epithelial destruction, 11% (7) due to exposure to toxins, 10% (6) due to trauma, 5% (3) due to congenital disorders, 5% from miscellaneous causes and 5% were psychiatric in nature.

The most interesting observations from this experience are as follows: First, the loss of smell is considered by all who suffer it a major disability. For these, food has lost its taste and, in a society that structures socialization around eating, this is a major handicap. Additionally, these patients cannot smell smoke and are not readily able to detect fires. Lastly, these persons cannot smell spoiled and rotten food and are at a higher risk for food poisoning.

CT scans were found necessary to evaluate the paranasal sinuses and were found to be superior to plain films in identifying ethmoidal inflammatory disorders. A short course of high doses of prednisone often returns the sense of smell to those whose disorder has an inflammatory cause and was found to be a useful diagnostic test. Neither zinc nor antihistamines were found to be useful treatments for patients suffering from anosmia.

Recommendations are that everyone suffering from anosmia have a complete evaluation. Those with an inflammatory cause are potentially correctable; those with other causes are not correctable, and patients need to be informed of their prognosis. All patients need to be advised of the necessity for smoke detectors and, for those using natural gas, propane or other gaseous substances, the need for in-house gas detectors. All need to be advised about the risk of spoiled foods.

Finally, some rehabilitation is possible, and just as the blind have learned to read with their fingers, those without smell can learn to taste through other senses.

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Microscopically Oriented Histologic Sections for Head and Neck Mucosal Cancer

Microscopically oriented histologic sections (MOHS) is a technique for frozen-section analysis of surgical margins. With the traditional pathologic orientation at frozen section, as little as 1/1,000th of a surgical margin may be examined, whereas with the MOHS approach, 100% of the surgical margin is purported to be examined. This technique has been successfully applied to the resection of aggressive nonmelanoma skin cancer and has become the standard of care for such lesions. This technique has now been applied to the local control of head and neck epidermoid cancers involving mucosal surfaces of the mouth, throat and upper airway. Experience at the University of California at San Diego Medical Center of 93 patients with two-year follow-up showed that the technique was highly effective in reducing the incidence of local recurrence. While there are no good data bases with which to compare these findings, and prospective studies are difficult to coordinate, it is recognized that 50% of the failures in the control of head and neck cancer are due to failure to resect and control local disease. In the 93 patients followed for two years, only 9 cases of local recurrence were reported, 3 of which were successfully treated with subsequent procedures.

The most important information to come out of this study concerned the biologic behavior of these tumors. It was observed that the tumors grew as an incontinuity growth and that

while there was an easily identified central mass of neoplasm, small fingers with diameters of five to ten cells were frequently identified, extending submucosally into surrounding and adjacent tissues for distances of up to 3 cm. Using MOHS as a technique of examining margins, tumor was found present 1 cm away from clinically evident disease in two thirds of the patients. Once identified, these small fingers or dendrites of tumor were easily traced and resected with additional directed excisions and microscopic examinations. The implications of this work are that by using this technique we should be able to better control local disease and therefore improve cure rates for head and neck epidermoid cancers. Additionally, there is implication that this technique may be useful in improving the local control rate for all neoplasms in which local control is a factor in morbidity and mortality.

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Computed Tomography in Head and Neck Surgery

During the past several years computed tomographic (CT) imaging of the head and neck has proved to be of great value to head and neck surgeons. Deep neck infections can be more accurately evaluated by delineating the presence of an abscess, its location and involvement of important surrounding structures. This helps a clinician to more accurately plan the surgical approach. CT may eliminate the need for an operation when jugular vein thrombosis, inflammatory lymphadenopathy or cellulitis is found.

When a mass lesion is present, CT may not only confirm the diagnosis but define deep tissue extent, facilitating surgical removal. It can also change the surgical approach by differentiating a cystic mass originating in the neck such as a branchial cleft cyst versus a cystic mass originating in the parotid gland. In some cases, this may be difficult to determine by clinical examination alone. It is considered to be the best single imaging examination in a patient with a lateral neck mass that is suggestive of branchial cleft cyst. If the mass is within the parotid gland, extension of the tumor into the deep lobe or into the parapharyngeal space can be found. This information may be crucial when selecting a surgical route.

Additional help in assessing benign disease may be obtained by differentiating congenital lesions such as cystic hygroma from branchial cleft cysts, paramedian thyroglossal duct cysts or an external laryngocele. Other deep neck neoplasms such as parapharyngeal space adenomas of salivary gland origin, benign neural tumors or vascular paragangliomas can also be diagnosed preoperatively because of their location, density or other specific characteristics.

In the initial evaluation of malignant disease, staging and treatment of the primary tumor and metastatic disease in the neck are aided by assessing the actual extent of the disease and its involvement of important surrounding structures. Follow-up examination of tumor response to therapy, diagnosis of tumor recurrence in the treated neck and the search for an unknown primary are all significantly enhanced by CT. In our experience, CT has been of particular help in patients who have a large primary tumor and a clinically normal neck. CT imaging has, therefore, become an integral part of the preoperative evaluation in head and neck operations.

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Endoscopic Sinus Operations

A radically different approach to the treatment of chronic or recurrent sinusitis has recently been introduced in the United States. The technique is not new, however, having been in use in Europe for ten years. The cornerstone of the theory behind this approach is that in chronic or recurrent sinusitis the problem is the anterior ethmoid sinuses. In patients with chronic or recurrent sinusitis, both diagnostic and therapeutic efforts are directed to this area. In severe cases, routine evaluation will show obvious sinus disease.

In patients with the appropriate history but unimpressive findings, however, further evaluation is indicated. This involves meticulous evaluation of the nasal cavity, especially the middle meatus, with sinus endoscopes, looking for purulent exudate, polyps or other abnormalities. In addition, computed tomographic scanning of the sinus is indicated. This is best done in the coronal plane, with the windows set as they are for lung parenchyma. The key abnormality is mucosal thickening in the anterior ethmoids.

Once disease in the anterior ethmoids is established, therapy is directed to that area. The key concept is a minimalist approach. In the operating room, under local or general anesthesia, an anterior ethmoidectomy is carried out under direct vision using the sinus endoscopes. The ethmoid bulla and infundibulum are opened into the middle meatus. If the remainder of the disease is reversible, nothing further is done. Beyond this point, only irreversibly diseased tissue is removed.

Over the next several weeks, the operative site will heal and the sinuses will re-aerate. During the healing period, frequent cleaning of the operative site is essential to prevent crusting or scarring from impeding drainage.

My experience over the past year validates this concept. A word of caution. Because visualization is so good with the endoscopes, it is easy to go farther than planned. Remember that the eye and the brain are close.

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Topical Gentamicin Prophylaxis with Tympanostomy

SINCE THE MODERN INTRODUCTION over 30 years ago of myringotomy with ventilating tube placement as a treatment for the various manifestations and complications of eustachian tube dysfunction, the use of this procedure has increased to where it is now reportedly done ½ to 3 million times per year. The most common complication is purulent otorrhea in the early postoperative period, occurring in from 10% to 34% of patients in various large series. Prompt resolution is the rule after one or more sessions of clearing the purulence and instilling otic drops in the ear of a more or less cooperative child. Oral antibiotics are often used also. The long-term consequences are minimal, but the inconvenience, anxiety and expense generated are significant.

Some authors and many practitioners have suggested and used various prophylactic techniques in attempting to minimize this troublesome problem. At least one prospective series has indicated that perioperative oral or topical administration of antibiotics may be useful, but statistical significance was not achieved. Our study is a randomized, prospective clinical trial comparing a single outcome variable: purulent otorrhea in the first 14 postoperative days in a control group (N=46) and a treatment group (N=56) that receives gentamicin ophthalmic drops in the ears for four days beginning in the operating room. Features of the history and management of the infected patients were also evaluated. Only a trend toward younger age in the patients and postoperative otorrhea were recognized.

Of the 102 patients, "early" purulent otorrhea developed in 9 and all of these were in the control group, thus yielding a *P* of greater than .001. It should be noted that the ototoxicity of topical propylene glycol and most of the antibiotics in otic drops has been established in animal models. Gentamicin is no exception. In years of experience with thousands of patients, however, neurosensory hearing loss has not been associated with the use of these preparations for this purpose.

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Photoactive Therapy for Head and Neck Cancer

THE PECULIAR PROPERTY of a number of organic compounds in biologic systems to respond to incident light by releasing energy has been known for a long time. Among the most active of these compounds are the porphyrins. The reaction of the skin of porphyria victims to sunlight with erythema and blistering is an example of the tissue-destructive effects of photoactivation. In recent times, this ability of porphyrins to release energy when activated by light has been exploited to selectively destroy tumors.

When hematoporphyrin derivative (HPD) is stimulated by light frequencies of between 400 and 600 nm, there is the release of a singlet oxygen radical that is toxic to tissues. In addition, a direct effect of the energy release results in changes in the plasma membrane of cells, causing cell death. In tumors, ischemic necrosis occurs due to destructive influences on the vascular supply.

Although photoactivation can be stimulated by a high-intensity white light, it is most effectively stimulated with the beam from an argon-pumped dye laser. A patient is injected with HPD at a dose of 3.0 mg per kg body weight, and the dye is allowed time to concentrate within the tumor (about 72 hours). The lesion is then exposed to 30 to 150 joules (watts per seconds) of laser light per cm^2 of tumor surface area. Over the ensuing 24 to 96 hours, the exposed tumor undergoes coagulation necrosis to a depth of 2 cm from the exposed surface. In another application of this technique, multiple areas of carcinomatous involvement of selected tissues are both detected and ablated, such as the multifocal basal and squamous cell carcinomas of sun-damaged facial skin or the "condemned mucosa" of the oral cavity in patients with field cancerization. Tumor sites are identified by "tuning" the dye laser to a frequency in the blue-green range that will cause the tumors to fluoresce (488 to 515 nm), then resetting the frequency to the red end of the spectrum that will cause necrosis (625 to 635 nm).

The most serious drawback of the technique is the problem of tumor specificity of the photoactive agents. Although tumors selectively take up HPD due to the vascular permeability of their capillaries, epithelial cells also bind the porphyrins, albeit to a much lesser but unfortunately significant degree. Therefore, a patient's skin remains sensitive to sunlight and strong fluorescent light for four to six weeks after injection. This problem can likely be circumvented—and specificity enhanced—by conjugating HPD with a tumor-specific monoclonal antibody. The antibody will selectively bind to the cell membrane of the malignant cell, but not to the neighboring healthy tissues. Laboratory experimentation directed to this objective is currently being actively pursued.

At present the use of this technique has been limited to diagnosing and treating multifocal basal cell carcinomas of the face and field cancerization of the oral cavity. Some clinical trials on larger tumors have been attempted with mixed results. Further modifications in the technology and methods of this therapy have great promise.

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Anterior Cricoid Split

NEONATAL INTENSIVE CARE units have come into being in the past 20 years. With these units, the use of prolonged endotracheal intubation is commonplace. The incidence of acquired subglottic stenosis is now estimated to be near 8% in premature infants who have had an endotracheal tube.

The subglottic space is unique in that it is encased by the circumferential cartilage of the respiratory tract, the cricoid cartilage. Mechanical irritation by the endotracheal tube causes mucosal edema, ulceration and granulation tissue formation. As the subglottic space is the only area that cannot expand to accommodate these changes, the injury to this area

is greater. Normally on extubation, this increased edema and granulation tissue are not enough to cause an airway problem. In some persons, however, the edema is severe enough to cause respiratory tract obstruction and requires reintubation. The factors that likely correlate with a higher incidence of acquired subglottic stenosis are duration of intubation, frequency of intubations, preexisting size of the subglottic space, concurrent infection, use of a ventilator, age and orotracheal instead of nasotracheal intubation.

Before 1980 the treatment of acquired subglottic stenosis was tracheotomy. In 1980 Cotton and Seid published their description of a new surgical procedure called the "anterior cricoid split" as an alternative to tracheotomy in selected children. In their series of 12 patients, 9 had successful extubation. Subsequent studies have shown similar results with some modification of the technique.

The procedure is very similar to a tracheotomy in terms of exposure. At this point, a vertical incision is made through the anterior wall of the cricoid cartilage and the first and second rings of the trachea and the underlying mucosa. With the endotracheal tube still in place, the cricoid cartilage normally spreads apart 1 to 2 mm, exposing the endotracheal tube. The incision is then closed over a small drain and the tube is left in place for 7 to 14 days. After this time, the child is returned to the operating room and the tube is removed.

To date, the anterior cricoid split is only recommended for anterior subglottic stenosis that is mostly of a soft (edema and granulation tissue) type. In most studies, a success rate of about 75% is obtained, although some children need to have a modified procedure done a second time. The report by Grundfast and co-workers suggests that the anterior cricoid split should only be done by someone experienced in pediatric airway problems with the help of an experienced pediatric or neonatal intensive care unit staff. Although the anterior cricoid split does not eliminate the need for tracheotomies, it is a valuable procedure that can avoid a tracheotomy in selected patients.

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Editorials

What About 'Private Practice'?

PRIVATE PRACTICE has long been an article of faith among many physicians. Those who choose to run for political office in organized medicine often use the preservation of private practice as a kind of slogan for their political platform. And there is a segment of the practicing profession that even now is trying to develop a political power base to "save" the private practice of medicine. The term private practice seems to have a high place in the group think of much of the medical profession. But few seem to ask themselves just what does the term mean, what is good or bad about it or what is its relevance to the way much of medicine is practiced and much of health care is delivered today.

For some, private practice equates with fee for service in patient care, and all that is good and bad about this system of payment. Proponents point out that only in this system is the doctor clearly working for the patient, since it is only the patient who pays the fee. They also point out that private practice, as exemplified in the fee for service system, best preserves privacy and confidentiality between doctor and patient, and is the system closest to what medical care is all about—that is, a patient who seeks help and a doctor who is willing and able to give help. And on the philosophical plane, it is held that the private practice of medicine fosters individual responsibility and individual freedom, or "free choice" on the part of patients. This system worked well in simpler times when there was more independence and less interdependence in patient care than exists today, and when physicians carried most of medical technology in their heads or in their black bags, and depended heavily on trust and confidence to bring what solace and comfort they could to their patients.

But the times have changed. There is now much more interdependence among physicians in the way they practice, and much more interdependence among physicians, their patients and the third parties that pay for much or all the care. In this new and much more interdependent world of health care, one may ask just how private can private practice any longer be? The word private can be defined as pertaining to an individual person, private as opposed to public (that is, government), or private, that is, not open to the public, as in private property. Clearly, in these terms there have been serious erosions into the traditional private practice of medicine. There has been an obvious trend toward depersonalization of the doctor-patient relationship, patient care is more open to peer and public scrutiny, and even the courts are publicly examining what happens in the "private" relationships between doctors and their patients. One can only wonder if private practice is becoming an empty slogan, or even an anachronism in this modern day.

In these days of high-tech medicine and of high finance in health care, there is a real and present danger that the personal and therefore private happening that occurs between a doctor and a patient, which is the very essence of medical practice, will be crushed by the massive steamroller of modern medical technology and the ever more bungling efforts in both the public and private sectors to limit the cost of health care. As traditional medical practice (and for many physicians this means private practice) is disassembled by modern technology and present-day economics, we must somehow see to it that physician responsibility to patient, confidentiality in patient care and the element of caring that develops in a personal relationship between doctor and patient are not lost, but rather preserved and strengthened. Patients, and especially sick patients, are in no position to do this. It can only be done by physicians, individually and through their organizations. What is needed is a rededication of the medical profession to the human side, if not the economics, of the private practice of medicine. This is both an individual and a professional responsibility of a high order. And it is still not too late to stem the tide. Or is it? Some affirmative action by physicians and organized medicine may be needed. It might make a significant contribution to the future of patient care.

MSMW

Is There an Exercise RDA for Health?

CURRENT ATTITUDES within the medical profession regarding the role of exercise in clinical practice vary widely. Claims are made by some physicians that exercise improves physical fitness but does nothing for health,[1] while others, having access to the same published information, promote exercise and physical fitness as a major preventive and therapeutic modality for various chronic degenerative diseases and psychological disorders.[2] However, thoughtful analysis of available data appears to have led most health professionals to the general conclusion reached by Phelps elsewhere in this issue: while exercise obviously is not a panacea, there are sufficient data to warrant carefully including it in an overall program of health promotion and to use it as part of a treatment plan for various medical conditions.[3,4] Major unresolved questions include (1) Does exercise cause an improvement in health or is being more active just another attribute of already healthy people? (2) What is the exercise stimulus required to improve clinical status? and (3) If a causal link exists, how much of what type of exercise is required to achieve specific health benefits?

Exercise and Functional Capacity

There should be no doubt that exercise training is the major clinical tool we have to increase functional capacity or physical fitness. Nearly all clinically healthy persons and ambulatory patients can increase their functional capacity by performing appropriately designed exercise programs. Such improvements in patients whose capacity limits their ability for self-care, gainful employment or quality of life should be considered an important aspect of comprehensive therapy whether or not they lead to a decrease in disease progression or mortality. The prescription of exercise for the maintenance or improvement in functional capacity will become even more important in the future as the average age of the patient population continues to increase.

Seeking a Causal Relationship

Due to the lack of adequately designed randomized clinical trials, most data supporting the contention that exercise leads to decreased morbidity and mortality come from prospective observational studies. A legitimate concern regarding these studies is that of selection bias. Did the inactive

people inherit a less healthy constitution, or are there differences in other health-related behaviors or personal characteristics that account for their generally higher risk? The first question is difficult to answer due to our lack of knowledge regarding the genetic basis for most chronic diseases and any inherited tendency to be more active. There is evidence that some aspects of carbohydrate and fat metabolism are partly regulated by features of skeletal muscle that have a major genetic component. Such traits may explain why even after several years of endurance training, previously sedentary men still do not show the same level of metabolic adjustment as successful endurance athletes. By analyzing subgroups of participants—such as smokers versus nonsmokers, normotensive versus hypertensive, normal weight versus obesity—and by multifactor analysis, it has been shown repeatedly that exercise is related to decreased medical risk independent of other known risk factors. However, not until we conduct randomized clinical trials of adequate size and duration will we know for sure if an increase in exercise by middle-aged men or women will cause a reduction in coronary heart disease, hypertension, type II diabetes or osteoporosis.

The Exercise Stimulus

If exercise causes specific health benefits, then there must be some defined stimulus that takes place as a result of performing the exercise that produces the change. Is the stimulus acute (occurring during or immediately after a single bout of exercise) or chronic (only occurring after repeated bouts of exercise)? Is the stimulus for any specific health effect mechanical, chemical, situational, social or some combination of these? Even though a great deal is known about the biologic changes resulting from exercise, we know very little about their controlling mechanisms or the stimuli to produce them.

The accelerated rate of energy production during exercise increases the rate of functioning of other biologic systems needed to support the raised metabolic rate of the skeletal muscles. Repeated stimulation of these systems will increase their capacity or efficiency. It is the adaptive response of these other systems, including the nervous, endocrine, hormonal, cardiovascular, respiratory and skeletal systems, that most likely provide many of the health-related benefits of exercise. Some of the health benefits may be related more to the physical or mechanical stress placed on muscles, connective tissue or the skeleton than to increased energy expenditure by the muscles. Changes included here are the maintenance of muscle tone and the retention of bone calcium following menopause.

Very little is known about how any psychological benefits are derived from exercise. Are the effects due to biochemical changes resulting from the activity itself, or are they behavioral and due to the interaction between the exercise and the exercising situation? Do psychological effects require a specific biologic change, such as a decrease in sympathetic nervous system activity, or can they occur due to a more behavioral stimulus such as physical separation from a stressful environment or a positive interaction with an exercise leader? The physical separation, pleasant surroundings or enthusiastic and attractive exercise leaders may be all that are required to decrease anxiety, hostility or depression. The actual biologic effects and thus the specific characteristics of the exercise required to enhance a psychological state may be of a lesser consequence than just the act of exercising.

How Much Exercise Is Required?

Extreme inactivity or immobilization produces numerous serious health consequences. These effects occur rapidly and are due both to supine posture and lack of movement. Changes include orthostatic intolerance, negative nitrogen balance, increased calcium excretion, decreased glucose tolerance, altered lipoprotein metabolism and skeletal muscle atrophy. Thus, there is good reason for the early and frequent activation of patients during a hospital stay or convalescence. It should not be concluded, however, that health improvements of a similar magnitude will be produced if already active people become even more active. The greatest health benefits from exercise are most likely derived by the very inactive.

For ambulatory patients and healthy adults, most training studies support the recommendation that the greatest health benefits are derived from frequently performing large-muscle, dynamic exercise at a moderate intensity relative to capacity. Such activity has been more effective than other types in favorably altering cardiopulmonary capacity and efficiency, lipoprotein and carbohydrate metabolism, fibrinolysis, insulin sensitivity and body composition. Activities fitting this category are many, including walking, hiking, jogging, swimming, cycling, rowing, selected sports or games and some around-the-house chores. The intensity ideally should be between 50% and 80% of capacity, but exercise at lower intensities probably provides some benefit. A goal for exercise duration is to target an energy expenditure of 300 kcal per session or 4 kcal per kilogram of body weight. For most people to expend this energy takes from 30 to 60 minutes, and they may have to build up to this level over several weeks or months. For recently sedentary adults, if exercise intensity exceeds 60% of capacity or 4 kcal per kg, then exercise sessions should be done every other day. At less than 60% of capacity or 4 kcal per kg, exercise might best be done five or six times per week.

Development of a pharmacopeia of exercise that can readily be applied by a clinician should continue. More definitive information needs to be provided on what the indications are for exercise therapy, how to cost-effectively assess a patient to individualize the exercise prescription and to determine when exercise should be proscribed to ensure patient safety. Major strides have been made in these areas for patients with coronary heart disease, but for most all other patients we still lack the information necessary to determine how they can best meet their recommended daily allowance of exercise.

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Cardiac Failure in the Peripartum Period Due to Myopathy of Unknown Cause

As early as the 1800s, an association between heart failure and the puerperium was made.[1] Cardiac failure occurring in

the peripartum period with no identifiable cause is classified as "peripartum cardiomyopathy" (PPCM). To establish this diagnosis, three rigid diagnostic criteria should be met:

- Occurrence of cardiac failure during the peripartum period,
- No previous history of heart disease and
- No specific cause identified.[2,3]

Whether this syndrome is a distinct entity, or part of an underlying condition exacerbated by pregnancy, is controversial.

The frequency of PPCM varies between 1 in 3,000 and 1 in 4,000 pregnancies. It occurs most frequently in older multiparous women. In the United States most reported cases have occurred in black patients, but all races are affected. Etiologic factors are difficult to identify. A possible association with nutritional deficiencies has been supported and subsequently questioned.[4]

Hypertension and the greater hormonal and hemodynamic perturbations seen in twin gestations are predisposing factors. Environmental stresses like heat and humidity seem to be more important in the pathophysiology of the disease than family history.[4] The cause of this disease may be an autoimmune process. The use of immunosuppressive therapy with steroids and azathioprine deserves further investigation.[5] Mortality has been estimated to range from 30% to 60%.

Clinical and pathologic reviews indicate that peripartum cardiomyopathy is a disorder distinct from other causes of cardiac failure. Myocarditis may indeed cause a dilated cardiomyopathy mimicking the signs and symptoms of the PPCM, but in this case a specific cause for the cardiac failure is found and the diagnosis of PPCM is not appropriate. Furthermore, the most frequent occurrence of PPCM is in the second (60%) and the first (37%) month in the postpartum period when the well-known increased susceptibility to viral infections associated with pregnancy is past. This disorder may be seen as late as the sixth month postpartum.

Symptoms of PPCM include fatigue, dyspnea, tachyarrhythmias, hemoptysis, edema and embolic phenomena. On physical examination, signs of cardiomegaly, rales or murmur as well as hepatomegaly and ascites are frequently observed. Chest radiographs usually confirm cardiomegaly, and electrocardiographic abnormalities are common. Anemia is occasionally present, but most laboratory data are nonspecific. Viral titers are essential to the investigative workup and are negative in patients with the PPCM syndrome. Echocardiography often shows dilatation of the left ventricle with decreased contractility. On occasion, a mural thrombus may be seen on a two-dimensional echocardiogram, in which case anticoagulant therapy should be started.

Invasive hemodynamic data obtained by balloon-tipped heart catheterization from women with this disorder are compatible with biventricular failure with preservation of an adequate cardiac output. Gross pathologic findings include cardiomegaly with ventricular hypertrophy and thickening of the endocardium. Mural thrombi, focal areas of myocardial destruction, fibrosis, interstitial edema and disintegration of the myocardial fibers are frequent findings.

What is the best recommendation for subsequent pregnancies? If cardiomegaly persists for six months after PPCM, future pregnancies are contraindicated and sterilization appropriate. If such a patient becomes pregnant, early termination is recommended, despite the risk of this procedure.

Most patients without residual cardiomegaly or ventricular dysfunction will do well with a subsequent pregnancy under careful monitoring. A team approach involving the obstetrician, a cardiologist or an internist is essential. Bed rest, digoxin, judicial usage of diuretics, sodium restriction, serial echocardiography and possibly anticoagulation are indicated. Even with such management, however, maternal mortality can be as high as 14%. This high mortality rate may in itself be seen as too high a risk and may not be acceptable to either the physician or the patient. Thus, the risk of future pregnancies needs to be individually assessed.

If ventricular dysfunction occurs at the time of delivery, invasive monitoring is recommended. Cesarean delivery should be reserved for standard obstetrical indications. If necessary, operative delivery can be done under continuous epidural anesthesia. The real challenge is in the immediate and late postpartum period, when thrombotic phenomena or arrhythmias can be fatal. If left ventricular function is substantially reduced after delivery, cardiac transplantation is a consideration.[6] Most authors believe that PPCM is not a contraindication to breast-feeding.

In summary, PPCM is a definite syndrome. The diagnosis is established, however, by excluding other recognized causes for cardiomyopathy. Strict criteria, as defined by Demakis and colleagues,[2] are necessary to correctly establish the diagnosis of PPCM. Every effort should be made to rule out other causes of cardiomyopathy, including immunologic studies and even endomyocardial biopsy. Additional efforts are also needed to further document the pathophysiology of this disorder.

Subsequent pregnancy should be considered only in women with resolution of the symptoms and disappearance of cardiomegaly within six months of delivery. Even patients with apparent resolution are at risk for recurrence. Judicious fertility counseling and closest clinical observation are required in any repeated attempt at pregnancy.

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Case Reports

Cough Due to Captopril

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CAPTOPRIL is useful in treating hypertension and as an "unloading" agent in managing congestive heart failure. It acts by lowering peripheral resistance and may do this in three ways: by inhibiting the "converting enzyme" that governs the conversion of angiotensin I to angiotensin II, by enhancing kinin levels (by inhibiting kininase II) and by influencing prostaglandin metabolism. The relative importance of these three mechanisms is not known but seems to vary with volume-renin state, the concomitant use of other drugs and undefined factors.[1]

Captopril therapy is useful because it is effective in most patients, is relatively well tolerated and lacks the side effects of many other antihypertensive drugs now available. The drug is, however, not without its problems.[2-8] Rash (5% to 10%), dysgeusia (4% to 7%) and gastrointestinal symptoms are its most common side effects, and neutropenia (0.2%) and proteinuria (1.2%) are rare complications. Renal failure is a hazard in patients with preexisting renal disease, especially renovascular disease. Side effects generally disappear when captopril use is discontinued and most seem dose-related, being less frequent at lower doses and often subsiding, despite continuation of therapy, when the dosage is reduced.[3] Recent work suggests that doses used in earlier studies may have been unnecessarily high.[3]

Cough due to captopril use has been reported in only a few series,[2,4-8] and the US manufacturer, Squibb, has had only desultory reports of this side effect (W. G. Jump, PharmD, E. R. Squibb, written communication, July 1985). Review of the published reports, however, suggests it is not uncommon, and my own experience is consistent with this impression. Cough has recently been described also with the use of enalapril maleate, a recently released, long-acting, angiotensin-converting enzyme inhibitor.[9]

I report four cases of cough almost certainly due to the use of captopril.

Reports of Cases

Case 1

The patient, a 59-year-old businessman, was seen in January 1985 because of cough. He had had hypertension for 25 years, but renal function was normal and he had no heart disease.

In March 1984, in the course of a routine medical evaluation, results of a pulmonary examination were normal and a chest film was negative. A spirogram was normal, with a forced vital capacity (FVC) of 3.85 liters (98% predicted), forced expiratory volume in one second (FEV_1) of 3.23 liters (84% of FVC) and a normal flow-volume loop. The pulmonary history was negative for smoking, asthma, frequent pulmonary infections and for chronic or recurrent cough until January 1984, when he had a respiratory tract infection complicated by severe sinusitis and otitis requiring myringotomies and, in August of the same year, antrostomies. A purulent postnasal drip, which had caused a nocturnal cough, cleared a few weeks after antrostomy.

In August 1984 his blood pressure was poorly controlled by a regimen of propranolol hydrochloride and hydralazine hydrochloride in daily doses of, respectively, 320 mg and 200 mg. On this regimen, he did not cough. Hydralazine therapy was then stopped and captopril, 75 mg a day, substituted for it; propranolol therapy was continued.

In October 1984 he consulted a chest physician because of a dry, almost incessant cough beginning several weeks earlier that interfered with sleep and with telephoning (an occupational necessity). Findings on pulmonary examination were normal. Methacholine challenge spirography showed FVC and FEV_1 values of, respectively, 3.66 and 3.07 liters (control), 3.43 and 2.89 liters after inhaled saline and 2.89 and 2.64 liters after 50 mg per ml of methacholine was inhaled, the drop in FEV_1 (3.07 to 2.64 liters) being 14% (a 20% drop is considered normal clinically). His cough exacerbated during the test but was immediately relieved by inhaling tebutaline sulfate. On the presumption that bronchospasm was causing the cough, a trial of prednisone, 30 mg a day, was given and his other medication regimen continued. The cough promptly disappeared but recurred when the prednisone dose was tapered after ten days. The propranolol regimen was then stopped and verapamil, 360 mg daily, substituted for it. The captopril use was continued, and his cough persisted unchanged.

From November 1984 to June 1985, the use of captopril (75 to 300 mg daily) was continued, and clonidine, spironolactone and metoprolol tartrate in various doses were combined with it. Cough continued unchanged except when captopril therapy was discontinued for two days, whereupon it disappeared within 24 hours and then reappeared two days after the drug therapy was restarted.

On June 4, 1985, his hypertensive daughter (case 2 below) told him that a hacking cough had developed shortly after she started taking captopril and that this cough had disappeared a few days after stopping it. When he reported this anecdote to me, he was advised to stop the captopril therapy immediately. Within a few days his cough had almost disappeared and, within three weeks, it had subsided completely.

On June 17, 1985, a regimen of labetalol hydrochloride was begun as his sole antihypertensive agent. A few weeks later, with a dose of 500 mg daily, a very slight cough appeared. This cough subsided in a few weeks without a change in medication and, as of October 2, 1985, it had not recurred.

At no point in his course had he been short of breath.

Case 2

This 25-year-old woman was the daughter of the patient in case 1. I did not examine or treat her but only interviewed her by telephone. She had had mild hypertension for several years. There was no history of heart or kidney disease, and

(McNally EM: Cough due to captopril. West J Med 1987 Feb; 146:226-228)

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in one second
FVC = forced vital capacity

she said she did not have chronic cough, asthma or significant lung disease and had never smoked. Initially she was treated with a regimen of propranolol (dose unknown) and thiazide. On this regimen she had no cough. Because it was ineffectual, propranolol therapy was stopped and captopril, 75 mg per day, substituted. A few days after she started taking captopril a cough developed that was dry, incessant and intolerable. She was not short of breath. After a month, she stopped taking the drug; a few days later, her cough disappeared. Treatment with atenolol, 50 mg per day, was then begun. Her blood pressure control has been excellent since and her cough has not recurred.

Case 3

This patient, a 63-year-old businessman, was seen January 1984 with thalamic stroke and untreated hypertension. Renal function was normal and there were no findings of heart disease other than minimal, nonspecific electrocardiographic repolarization abnormalities. He said he did not have cough or dyspnea and his chest film in October 1984 had been normal; he had smoked cigars and pipe only until eight years before, and a mild cough disappeared then and did not recur.

He was initially treated with β-blockers (propranolol, 80 mg a day, then nadolol, 40 mg a day), but this therapy was stopped because of depression; he did not cough while receiving these drugs. In April 1985, therapy with captopril, 75 mg a day, was begun and a week later the dose was increased to 100 mg a day. Blood pressure control was excellent. On July 8, 1985, he reported a dry, incessant cough that kept him awake; it had begun about a month earlier. He was not short of breath. Cardiopulmonary examination showed no abnormalities. Methacholine challenge spirography showed FVC and FEV_1 values of, respectively, 2.49 liters (80% of predicted) and 2.36 liters (95% of FVC), controls; 2.40 and 2.11 liters after inhaling saline, and 2.53 and 2.09 liters after inhaling 50 mg of methacholine, the decrease in the FEV_1 (2.36 to 2.09 liters) being 10% (a 20% drop considered normal clinically); neither dyspnea nor cough occurred with the test.

The use of captopril was then discontinued, and the cough subsided in 72 hours. On July 20, 1985, at his own insistence, the captopril therapy was resumed. Within three days his cough had recurred. A few days later he stopped taking the drug, and again within three days the cough subsided.

Nifedipine was then given with good blood pressure control and no significant side effects. His cough did not recur.

Case 4

This 56-year-old woman presented in mid-January 1985 with dilated cardiomyopathy. She complained of dyspnea, anginal chest pain and fatigue with effort. She had for some time been taking digoxin and a diuretic. In February 1985 a regimen of captopril, 37.5 mg a day, was begun and a month later the dose was increased to 75 mg a day. Her dyspnea was much relieved. On May 23, 1985, she mentioned a slight dry cough that had begun about two weeks earlier. This was attributed to left ventricular failure and the dosage of captopril was increased again, to 100 mg a day. On August 21, 1985, her condition was stable in every way but she again noted dry cough that had worsened and had now become very annoying. Aware now that the use of captopril can cause cough, I stopped the drug therapy abruptly. Within three days the cough was "much better" and on September 10 it was gone. After discontinuing the captopril regimen, her effort dyspnea gradually worsened but she felt otherwise about the same.

Discussion

In these four patients, cough began a few days to weeks after captopril therapy was started (see Table 1), persisted until the drug regimen was stopped and then subsided quickly, with remarkable improvement in two or three days and complete disappearance in no more than a few weeks. Doses were average. The cough was dry, mild to moderate in severity, but intolerable in three patients because it kept them awake and, in one of these three, also precluded phone conversations necessary in his work. No patient was short of breath.

There is little doubt that cough in these four patients was indeed due to the use of captopril. Especially convincing was case 3, in which the patient's cough recurred when he resumed taking captopril and disappeared when the therapy was stopped the second time. This response occurred also in the case reported by Sesoko and Kaneko, in which the drug therapy was resumed and discontinued twice. None of the four patients in the cases reported here had cough before or after the captopril experience except in case 1 in which the patient had a transient, slight cough with a regimen of labetalol (though he had had none with a large dose of propranolol).

The frequency of cough due to captopril therapy is not established, but the scant published data suggest it occurs in about 5% to 15% of patients treated for a long time with the drug, an estimate consistent with my experience. If this estimate is correct, cough may well be the most common side effect of this drug. Havelka and co-workers cite 4 cases of 67 patients treated over a long term with a regimen of captopril, with disappearance of cough within three weeks of stopping the drug therapy in the one patient who did so.[4] Forslund and associates mention cough in one of ten patients but give no details.[5] Knoben reports 45 cases in which 7 patients had cough that, in all 7, subsided within a few days of stopping the captopril therapy and recurred within a few days of resuming it.[7] In three cases, cough was so severe that the drug therapy had to be stopped. My own experience of finding two new cases within three months of being alerted to the problem (by the first two patients) suggests that cough is rather a common side effect of administration of the drug. Yet Frohlich and colleagues, in their extensive review of the captopril experience, do not mention cough as a side effect.[3]

The cause of cough in these patients is not clear. Congestive heart failure is unlikely: three had no heart disease, no dyspnea and no signs of congestive heart failure at the height of their cough; and case 4 (with cardiomyopathy) was, in fact, *less* breathless while on a regimen of captopril than after stopping it. Pulmonary infiltrates were unlikely, in view of the lack of physical signs and the rapid disappearance of symptoms on discontinuing taking the drug, but chest films were not done and this source cannot be ruled out.

Bronchial irritability is theoretically an attractive explanation of captopril-induced cough. This drug inhibits the angiotensin-converting enzyme, which is identical to (pulmonary) kininase II. Kininase II governs the catabolism of bradykinin,

TABLE 1.—*Clinical Characteristics of Patients on Captopril Therapy*

Case	Age, Years	Sex	Diagnosis	Heart Disease	Lung Disease	Captopril Dose, mg/d	Remarks
1 . . .	59	♂	Hypertension	No	No	75	No cough with β-blocker
2 . . .	25	♀	Hypertension	No	No	75	No cough with β-blocker
3 . . .	63	♂	Hypertension	No	No	100	No cough with β-blocker
4 . . .	56	♀	Cardiomyopathy	Yes	No	75	Dyspnea less with captopril

and inhibition of this enzyme would be expected to increase bradykinin levels in the lung.[1,10] This increase might affect the lung by directly inducing smooth muscle contraction, by promoting local edema or by irritating nerve endings. By stimulating phospholipase, bradykinin could augment formation of the arachidonic acid derivatives, prostaglandins and leukotrienes, which may be etiologically important in asthma,[1,11] and it may also directly affect release of histamine from mast cells, an action thus far shown, however, only in murine mast cells in vitro. Inhaling bradykinin can provoke bronchospasm, but only in patients with asthma[12]; none of the patients in the cases reported here had asthma.

In case 1, bronchial irritability is suggested by the exacerbation of cough by methacholine and its termination with the use of the β_2 agonist, terbutaline, during the methacholine challenge; by the unequivocal relief of cough with the administration of prednisone, and, perhaps, by his slight cough on labetalol therapy alone. At the height of his captopril cough, however, he was not short of breath with effort, had no physical signs of bronchospasm and spirography results were only slightly, if at all, positive for bronchospasm before or after methacholine challenge. Moreover, his cough while receiving a substantial dose of labetalol was mild and transient, whereas the captopril-associated cough had been insufferable; indeed, he had had no cough at all while taking propranolol, 320 mg daily. The patient in case 3 had no cough with substantial doses of both propranolol and nadolol, but a severe cough developed on two occasions with the use of captopril; his spirogram findings were also unimpressive. The patient in case 2 had no cough on an atenolol regimen of 50 mg a day.

A practical implication of this experience is that, in patients in whom cough develops while on captopril therapy, β-blockers need not be withheld on the presumption of provocable bronchospasm.

Cough due to captopril therapy is not common and is probably idiosyncratic. Its concurrence in father and daughter (cases 1 and 2), therefore, suggests a genetic determination.

Captopril may be easily overlooked as the cause of cough. In a patient with heart failure "unloaded" with captopril therapy, cough is likely to be ascribed to the failure itself and the drug therapy continued or even increased, as initially in the patient in case 4. In a hypertensive patient taking a β-blocker and captopril, cough is likely to be attributed to the β-blocker, as in case 1, or to occult heart failure, whereupon the captopril dose might be increased.

Prospective studies can establish how often captopril causes cough, which patients are likely to get it, the role of dose and possibly even the cause. Such studies are feasible because this excellent drug is often used and cough, when it occurs, does so soon after starting captopril therapy and subsides promptly on stopping it.

Addendum

Since this report was submitted, three other cases of captopril-induced cough have come to my attention. The first was of a 70-year-old woman with hypertension in whom a severe cough without dyspnea or wheezing promptly developed with the use of captopril, 50 mg per day, and whose cough completely disappeared two days after stopping the therapy several weeks after beginning it. The second case was of a 72-year-old woman with hypertension and ischemic heart disease complicated by mild congestive heart failure and mild mitral regurgitation who, in 1982, while receiving an unknown dose of captopril, had a cough develop that cleared completely five days after the drug therapy was stopped. In November 1984, after captopril therapy was resumed at 75 mg daily, a cough developed that disappeared a few days after she stopped taking the drug. The third patient, a 63-year-old woman with hypertension and a questionable history of asthma, had the development of an annoying cough without dyspnea on a regimen of captopril, 75 mg daily. The cough cleared over a two-week period after stopping the regimen; she is currently under investigation for airways disease.

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Stress-Induced Cessation of Lactation

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ANECDOTAL REPORTS of abrupt cessation of lactation due to psychological stress are well known in folk experience. In this paper I describe the cases of two women who had abrupt cessation of lactation and of colostrum excretion, respec-

(Ruvalcaba RHA: Stress-induced cessation of lactation. West J Med 1987 Feb; 146:228-230)

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tively, following the psychological stress experience of the 1985 Mexico City earthquake.

Reports of Cases

Case 1

The patient, a 24-year-old woman, was examined 12 days after the earthquake occurred in 1985. She was gravida 3, para 3. Her 3-month-old infant girl was being exclusively breast-fed by the patient. She had been successful in breast-feeding her 5- and 3-year-old sons until the ages of 14 and 18 months of age, respectively. The mother stated that early on the morning of September 19, 1985, she walked to the market located three blocks from her address, leaving her children at home unattended. At 0718 hours, the Mexican earthquake struck and part of the market's roof came down and injured several people. She became frightened and concerned for the safety of her children and ran to her house. On her way she saw several demolished buildings and she heard the cries of the injured, which further distressed her. On arriving at her house, she found all the children crying but unharmed and her home intact. She attempted to nurse her infant girl but, to her surprise, did not have the usual sensation of the "let-down reflex." The infant was not able to obtain milk in spite of vigorous nursing. The infant continued to cry and further attempts at nursing throughout the day failed to pacify her. Later in the day the mother procured a commercial milk formula to nourish her infant. Further breast-feeding attempts for the next week did not produce milk. She described herself as being "very nervous and upset" since the day of the earthquake. No abnormalities were noted on physical examination. Expression of her breasts failed to produce milk.

Case 2

The patient, a 35-year-old gravida 4, para 3 woman, was examined 16 days after the earthquake occurred. She presented to the clinic on the 39th week of gestation due to her concern of possibly being unable to breast-feed her unborn infant. She had breast-fed her previous three children successfully beyond the first year of life. Her current pregnancy had been uneventful and, as in previous gestations, she noted spontaneous copious discharges of colostrum throughout the last couple of months before delivery. In this pregnancy, the colostral discharge was also abundant, requiring her to wear padding in her bra to prevent wetting of her clothing.

On the morning of September 19, 1985, at about 0645 hours, her husband and her 8- and 6-year-old children left home, and she was left with her 3½-year-old daughter. At 0718 hours the earthquake occurred, seriously damaging her home. One of the rooms was completely destroyed. Several falling bricks struck her on the right arm, causing ecchymosis and abrasions; her daughter was unharmed. They ran outside their house where she saw a several-story high apartment house that was completely demolished. She did not know whether or not her husband and other children were safe until several hours later; they were unharmed. Her younger sister and husband had died when their apartment collapsed. Since that day, she and her family have been housed at another sister's three-bedroom apartment, which was also being shared with another family, for a total of 15 people.

On the day of the earthquake, the patient noted that the padding in her bra was not wet. She has not noted leaking of colostrum since that time. She has suffered from insomnia, anorexia and nervousness. Findings of a physical examination were normal for a woman at term gestation. Expressing the breast yielded only a few drops of colostrum bilaterally.

Comment

Lactation in a normal woman is under the control of various reflexes, including the nipple erection reflex with tactile and psychogenic components, the prolactin reflex mediated through the cortical-hypothalamic influence on the anterior pituitary secretion of prolactin and, finally, the let-down reflex, which is mediated via nipple stimulation and psychogenic factors. The cortical pathways act on the paraventricular nucleus of the hypothalamus and subsequent posterior pituitary secretion of oxytocin. Prolactin facilitates the filling of the breast with milk, and oxytocin activates the contraction of the myoepithelial breast alveoli "basket cells," filling the terminal lactiferous ducts and resulting in the ejection of milk.[1]

The two women in this report clearly had abrupt cessation of milk and colostrum secretion, respectively, immediately following the major psychological stress caused by the earthquake experience. The initial failure of the let-down reflex on the lactating women was followed by further stress caused by the frustrating experience of a hungry, dissatisfied, crying infant. The pregnant mother near term, who, as in previous gestations, was leaking colostrum, noted that its secretion ceased abruptly for at least 16 days after the catastrophe when the examination took place. This woman's stress was prolonged by her grief reaction to the death of her sister and the crowded living conditions. Unfortunately, I do not have any information on the outcome of lactation after delivery.

Tension, fear, discomfort or embarrassment can inhibit the milk ejection reflex of lactating women.[2] Veterinarians are aware of the inadequate lactation or failure of the let-down reflex on stressed cows,[3,4] and the same phenomenon has been observed in laboratory animals.[5,6] Stress inhibition of oxytocin secretion is believed to be mediated centrally through neurohumoral, noradrenergic, cholinergic and dopaminergic mechanisms.[7-9] Dopaminergic effect also suppresses prolactin secretion (prolactin inhibitor factor).[10] Stress-related inhibition of the milk ejection reflex might also result from peripheral α- and β-adrenergic effects. α-Stimulation causes vasoconstriction in the breast area that prevents oxytocin access to the mammary myoepithelial "basket cells." The β-receptor stimulus dampens the myoepithelial action and increases the tonicity of the mammary ducts.[11,12]

Cessation of spontaneous colostrum secretion observed in the pregnant woman was probably not due to lack of the lactogenic hormone. The placenta supplies prolactin during the last trimester of gestation. The mechanism may be related to oxytocin or local α- and β-adrenergic effects in the breasts, or both.

These cases illustrate the role that psychological factors play in lactation; stress appears to hinder the production of milk. The mother requires a stable, calm environment for successful lactation, as well as supportive, empathic spouse, family and physician.

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Peripartum Cardiomyopathy—Successful Treatment With Cardiac Transplantation

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MANY CASES and studies of peripartum cardiomyopathy have been reported but the etiology and natural course remain unknown. The first description of this disorder was made by Ritchie in 1849 and, based on Meadows's description in 1960, it has also been known as "Meadows's syndrome."[1] Subsequently the disorder has been characterized on clinical, hemodynamic and histologic bases, but a diagnosis remains one of exclusion. The disorder apparently affects less than 1% of all patients suffering cardiac diseases of pregnancy, but it is associated with significant fetal (10%) and maternal (30% to 60%) mortality.[1,2] Peripartum cardiomyopathy affects women during the last trimester of pregnancy and during the early postpartum period; therefore, the name "peripartum" (as opposed to "postpartum") cardiomyopathy is most appropriate.

The criteria for diagnosis include the development of heart failure during the last month of pregnancy or during the first three to six postpartum months, absence of other causes of heart failure and absence of any heart disorder before the last month of pregnancy.[3-6] The clinical course of the disease is quite variable and severity appears to be indicated by whether or not the heart size returns to normal within six months.[5,6] Although pathologic findings are similar, patients whose heart size does not return to normal have a greater morbidity and mortality than those whose heart size does return to normal. The outcome of subsequent pregnancies was also poorer in the former group.[4,5]

The following case report shows some of the serious potential complications experienced by a woman with peripartum cardiomyopathy. Her course is one of rapid decline ending in morbid congestive failure, which necessitated an orthotopic heart transplantation. She is currently convalescing well without adverse consequences.

(Joseph SG: Peripartum cardiomyopathy—Successful treatment with cardiac transplantation. West J Med 1987 Feb; 146:230-232)

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The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Report of a Case

The patient, a 27-year-old woman who was gravida 2, para 2, was admitted to 5th General (US Army) Hospital, Stuttgart, West Germany, seven days after normal spontaneous vaginal delivery of a healthy male infant. She complained of fever, chills, nausea, vomiting and subsequent increased vaginal bleeding. She also noted a progressive shortness of breath beginning about 48 hours before admission.

The patient had been delivered of her first child 12 months previously, and both pregnancies were normal. During the second pregnancy, however, she was noted to have rare multifocal, premature ventricular contractions on routine and 24-hour ambulatory electrocardiograms (ECGs). Physical examination during her early third trimester revealed no definitive heart disease; no antiarrhythmic drugs were used, and the patient was followed until delivery with no development of complications. She specifically said she did not have any symptoms of congestive heart failure. She had no significant past medical history; indicated no use of alcohol, cigarettes or illicit drugs, and reported no hypertension, toxin exposure or peripartal illness. Family history revealed that her mother had a myocardial infarction at age 53. The patient's predelivery weight was 61 kg (134.5 lb).

On admission to the hospital, a physical examination initially elicited clear lung sounds, and no cardiac abnormality was noted. Temperature was 38°C (100.4°F), blood pressure 100/70 mm of mercury supine and respirations 30 per minute, with a heart rate of 100 per minute. On pelvic examination her uterus was soft, nontender and she had normal adnexa. Hematocrit was 35%, leukocyte count was 16,000 per μl with 30% band forms and platelets were 106,000 per μl. Electrolyte values were normal, blood urea nitrogen level was 16 mg per dl and creatinine level was 1.2 mg per dl. She was placed on a regimen of ampicillin, gentamicin sulfate and clindamycin (Cleocin) hydrochloride for presumed endometritis.

Twelve hours after admission increased shortness of breath developed, with bibasilar rales, greatly elevated jugular venous pressures, hepatojugular reflux and facial plethora. On cardiac examination she had normal first and second sounds, with third and questionably fourth heart sounds heard. There were no murmurs. The abdomen was soft, but with guarding in lower abdominal segments. The extremities did not show cyanosis or edema. A chest x-ray film revealed an increased cardiothoracic ratio, a cephalized vascular pattern and interstitial edema. An ECG showed nonspecific ST-T-wave changes that were unchanged from those during pregnancy; there was no ectopy. A suboptimal echocardiogram showed a small pericardial effusion but no mural thrombosis. A Swan-Ganz catheter was placed in the right side of the heart, with pressures as follows: right atrium 20 mm of mercury, pulmonary artery 51/38 mm of mercury with a mean of 40, pulmonary capillary wedge pressure 23 mm of mercury, cardiac output 3.1 liters per minute (cardiac index 1.92 liters per minute · m^2); systemic vascular resistance was 1,560 dyne seconds · cm^{-5}, and pulmonary vascular resistance was 440 dyne seconds · cm^{-5}. The blood pressure was 100/60 mm of mercury.

The patient was treated with inotropic agents given

orally and intravenously, and antibiotic therapy was continued for presumed peripartum cardiomyopathy and endometritis, respectively. During the next 48 hours, the platelet count fell, the prothrombin and partial thromboplastin times increased and liver function abnormalities developed with elevated aminotransferase levels. Fibrin-degradation products were elevated and the fibrinogen level was depressed—all consistent with a disseminated intravascular coagulopathy.

Six days after admission, the patient's blood pressure fell dramatically, accompanied by severe hypoglycemia (32 mg per dl), hyponatremia and precipitous hyperkalemia (127 mEq per liter from 134, and 6.2 mEq per liter from 4.7, respectively, several hours previously). The patient was felt to be in an acute adrenal crisis and responded dramatically to a regimen of 50 ml of 50% dextrose and 8 mg of dexamethasone given intravenously. The latter was changed to 250 mg of hydrocortisone given intravenously every six hours pending base-line cortisol levels, for which specimens were drawn before dexamethasone was administered. Several hours later, evidence of a thromboembolic event developed in the patient's lower extremities, with pallor, pulselessness, pain and partial paralysis. Heparin was given intravenously, with resolution of the lower extremity pain and pallor and return of pulses within 12 hours.

A repeat ultrasound examination of her pelvis showed retained intrauterine contents, which were found at limited dilatation and curettage to be necrotic decidua. Cultures of this tissue grew *Enterococcus* and *Staphylococcus epidermidis,* and an appropriate antibiotic regimen was instituted.

Subsequently, liver and renal function returned to normal, but the hematocrit slowly fell to 27% and stabilized. There was no apparent source of blood loss. Diuresis ensued and her weight fell from 73 kg (160 lb) to 66 kg (146 lb). Cortisol levels were found to be supranormal and steroid administration was discontinued. Her condition improved hemodynamically and she was weaned from inotropic and vasodilator therapy. By the 20th day in hospital, she was able to ambulate with minimal exertional dyspnea and had no further paroxysmal nocturnal dyspnea. She continued to require two pillows for restful sleep.

The patient was then transferred for further cardiac evaluation, where radionuclide-determined ejection fraction was found to be 10%. Before transfer she was clinically in functional class III (using the New York Heart Association's classification). There was no isolated wall motion abnormality, but global hypokinesis was present. Pericardial effusion, seen earlier, had resolved. She manifested intermittent prolonged ventricular tachycardia and required treatment with lidocaine hydrochloride and later with tocainide hydrochloride and quinidine gluconate.

She subsequently experienced further shortness of breath at rest, and further decline of cardiac function was noted, placing her in functional class IV. She was then evaluated for and received a four-locus allogeneic orthotopic cardiac transplantation. The patient is recovering without complication and with good exercise tolerance at 19 months after transplantation. She is currently on a regimen of azathioprine, prednisone and cyclosporine after several episodes of clinical and biopsy-proved rejection. Pathologic findings of the native heart included moderate myocardial hypertrophy, a small area of healing subendocardial myocardial necrosis, patchy myocyte loss, organizing mural thrombi, moderate endocardial fibroelastosis and minimal coronary artery atherosclerosis. The changes, while not severe nor specific, are consistent with idiopathic dilated cardiomyopathy.

Discussion

This case is illustrative of many of the common factors of this disorder and of the complications that may ensue. In addition, however, many of the less common epidemiologic and clinical features were present and will be discussed. The occurrence in this patient of disseminated intravascular coagulation and the impression of adrenal insufficiency (later disproved), while not characteristic of the illness, shows some of the associated perils of peripartum cardiomyopathy.

The syndrome remains a rarity, occurring in about 1 in 3,000 to 4,000 pregnancies, and accounts for less than 1% of the cardiac disorders associated with pregnancy.[1] A common variation of this syndrome has been reported by Ceptin and co-workers,[7] Sanderson and associates[8] and Filmore and Perry,[9] the last cases occurring in Zaria, Nigeria, in which volume overload appears to be etiologically involved. This may be due to the unusual dietary and postpartum practices of the study group, which include excessive salt intake and the use of a heated bed and hot baths. Indeed, these latter factors may violate the criterion of absence of other causes of heart failure. Other factors that may have a deleterious effect on the outcome of pregnancy include poor nutrition, alcoholism, prior disease and prior use of drugs.[2]

In his review of the syndrome,[10] Veille points out the common epidemiologic factors of this disease, some of which were shared by this patient. He notes that the syndrome occurs more frequently in older and multiparous women. There is also a greater frequency of occurrence in nonwhites, women with multiple gestations and in those with poor nutrition. Older women seem to be more prone to peripartum cardiomyopathy, with 48% of all victims being 30 years of age or older.[4] Also, toxemia occurred in 22% of women with the disorder, a rate five times higher than in pregnant women without it.[5] The etiology of the syndrome remains unclear, although some claim that myocarditis of various causes may trigger peripartum cardiomyopathy.[6,11,12] The role of hypertension remains debated, although many cases, including this one, involved normotensive or only mildly hypertensive patients. Many of the larger reports involve cases in tropical or subtropical areas, suggesting the possibility of social, infectious, dietary and other factors as etiologically important.[8,9,13] These factors, and those of toxin exposure and drug and alcoholic cardiomyopathy, need to be excluded to meet the criteria for peripartum cardiomyopathy as mentioned above.

This patient's presentation was fairly typical in that breathlessness, tachycardia and edema occurred, associated with cardiomegaly and radiographic evidence of congestive heart failure and pulmonary edema. Findings of catheterization of the right side of the heart were consistent with those reported by Ceptin and co-workers,[7] although her cardiac index was somewhat more depressed. ECG changes were nonspecific, as were pathologic findings, also typical of other reported cases. Light microscopy and electron microscopy were reported to show no significant

difference between peripartum cardiomyopathy and congestive cardiomyopathy of other causes.[4,14]

The natural history of the disease is variable with no immediate predictors of severity or prognosis. The long-term prognosis, however, is noted to be related to return of the heart size to normal with 50% of patients having such within the first year postpartum.[4,5,13] Walsh and associates, however, reported that only 20% of their series had a return of heart size to normal.[15] Of note in this patient group was the poor nutritional state compared with the group reported by Demakis and colleagues.[5] As seen in this latter series, patients with cardiomegaly beyond six months after onset have a very poor prognosis. Of the 13 such patients, there was less than 50% five-year survival, with an average length of survival of 4.7 years after the first episode of cardiomyopathy. Other authors report even higher mortality figures.[13,15] In these series, frequent complications included pulmonary embolus, supraventricular arrhythmias, systemic embolization and recurrence or exacerbation during subsequent pregnancies.

Although Demakis points out that many patients whose heart size returned to normal could then return to normal activity, many were also found to have electrocardiographic or histologic markers of heart disease and a third remained in functional class II.[4] Although many authors have maintained that subsequent pregnancies are likely to have similar complications,[1,13,15] Demakis noted that pregnancy was well tolerated in those patients whose cardiothoracic ratio returned to normal.[5] Of 8 of such patients having 21 subsequent pregnancies, only 2 had temporary cardiac dysfunction during three pregnancies. In contrast, of six patients with persistent cardiomegaly who again became pregnant, half had severe and permanent cardiac deterioration that resulted in death.[5]

The therapy for peripartum cardiomyopathy is similar to that for congestive heart failure from other causes. These patients are frequently noted to be sensitive to the effects of digitalis, and extra caution in its use is therefore merited.[6,16] The high incidence of pulmonary and systemic emboli prompts many to recommend anticoagulation for the duration of the cardiomegaly.[5] Appropriate limitations of life-style should correspond to the degree of cardiac disability and should correlate with heart size. Because of the likelihood of fatal deterioration with subsequent pregnancy in patients with enlarged heart size, appropriate birth control measures should be recommended in those patients. Estrogen-containing oral contraceptives should be avoided, however, because of their increased contribution to the incidence of pulmonary emboli. Burch and colleagues recommend prolonged bed rest in an effort to improve the prognosis of peripartum cardiomyopathy.[6] Their results, however, are comparable to those of other investigators[4,5,13] who do not use the three- to six-month bed-rest regimen. Immunosuppressive therapy may be useful for those patients in whom an inflammatory myocarditis is either strongly suggested or confirmed by endomyocardial biopsy.[11]

As transplantation expertise has grown over the past decade to include the use of potentially less toxic immunoregulators,[17] this method of therapy has become even more attractive for rapidly deteriorating patients such as the one described here. Patients with only a modest reduction in cardiac function manifested by a less severe symptom complex should continue to be treated conservatively because their prognosis is excellent if heart size returns to normal.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Human Immunodeficiency Virus and Hepatitis Testing of Old Bottles of Plasma

To the Editor: It has been stated by Allen and co-workers[1] that between 5% and 20% of all plasma pools made during World War II and for some time thereafter transmitted serum hepatitis. These pools were made from a large number of donors, often as many as 1,000 or more, and thus if one of these donors carried the hepatitis virus the entire pool would be infectious. If the plasma was lyophilized the infectivity was preserved for extended periods of time.

Nine years ago we reported on the chemical analysis of a 30-year-old bottle of lyophilized plasma.[1] This unit had been preserved as a quality control standard by being lyophilized and having its neck closed by heat sealing. We found that the protein was easily soluble and that most of the enzymes and protein constituents were unchanged or only slightly decreased in activity. We also found that the unit was positive for hepatitis B surface antigen (HBsAg) by radioimmunoassay techniques although negative by counterelectrophoresis.

Recently one of us (CHB) obtained several more 30- to 35-year-old units of plasma. Each bottle was from a different pool of plasma. They were from several manufacturers and were sealed with rubber stoppers that had cracked with age. The outdates of the plasma were between 1956 and 1958 and these outdates were usually five years after the processing. These would have been prepared, and many of the bottles from each lot used, during the Korean War. We were interested in testing these units for the human immunodeficiency virus (HIV, previously designated HTLV-III or LAV) markers, and also for other markers of hepatitis not available at the time of our previous study.

Four units appeared in relatively good condition and were analyzed. All four dissolved poorly and a moderate amount of the proteinaceous material never did dissolve. Electrophoresis of some of the soluble material showed a continuous band of proteinaceous material with no distinct peaks indicating severe denaturation. An aliquot was taken from this material and was analyzed for the HIV and hepatitis markers (see Table 1). The HIV marker reacted in an equivocal manner with slight activity but not enough to be considered positive. We feel that this reactivity is probably due to the poor nature of the material being tested. All of these pools were positive for the hepatitis B core (HBc) total antibody, while none reacted with the hepatitis B core-IgM antibody (HBc-IgM). One was clearly positive for hepatitis B surface antibody (HBsAb) and two were positive for HBsAg. One was positive for the hepatitis Be antigen (HBeAg). All were negative for delta agent.

It has been well established by a number of investigators that pooled plasma retains its infectivity for a long period of time. We were interested to see that these units although stored improperly for 30 to 35 years retained their reactivity for most of the markers used for hepatitis testing today, and were nonreactive for HIV antigens. Previous history has shown that these samples were infectious for hepatitis so this correlates well with the hepatitis markers. We do not feel that we can offer an opinion on the correlation of infectivity and the lack of the HIV antigen on the basis of the few lots tested.

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TABLE 1.—*Results of Analysis for HIV and Hepatitis Markers*

	Normal Human Plasma Lot# 10696 21 July 56 Irradiated, Dried Courtland Lab.	*Normal Human Plasma Lot# B-1391-2 18 Oct 56 Irradiated, Dried Sharp & Dohme*	*(Not for Human Use) Normal Human Lot# 3380 3 Feb 58 Treated w/Clm Courtland Lab.*	*Normal Human Plasma Fractions, Lot# 24261 (Outdate Illegible) Heat Treated, Courtland Lab.*
HIV Antibody	Equivocal	Equivocal	Equivocal	Negative
Hepatitis B surface antigen (HBsAg)	Positive	Positive	Negative	Negative
HBsAg confirmation	Positive	Positive		
Hepatitis Be antigen (HBeAg)	Negative	Positive		
Hepatitis Be antibody (HBeAb)	Negative	Negative		
Hepatitis B core antibody (HBcAb)	Positive	Positive	Positive	Positive
Hepatitis B core-IgM antibody (HBc-IgM)	Negative	Negative	Negative	Negative
Hepatitis B surface antibody (HBsAb)	Equivocal	Negative	Positive	Negative
Hepatitis delta antibody	Negative	Negative	Negative	Negative

Lysosomotropic Agents in AIDS Treatment

To the Editor: There is currently considerable interest in the etiology, diagnosis and treatment of the acquired immunodeficiency syndrome (AIDS). While the incidence of AIDS continues to increase exponentially, there is no currently proved treatment or prophylactic agent.[1] Substantial evidence has accumulated to implicate a novel retrovirus—human immunodeficiency virus (HIV)—in the pathogenesis of AIDS. This virus appears to have a tropism for helper T lymphocytes expressing the T4 (CD4) antigen, and the cytopathic effect of the virus on helper T lymphocytes accounts for the major clinical manifestations of AIDS.[1] A recent report[2] suggested that the T4 antigen is in fact the cell surface receptor for the AIDS virus and that the virus subsequently enters the cell via endocytosis. The process of receptor-mediated endocytosis has been well characterized for a number of proteins, hormones, toxins and viruses, including retroviruses.[3-6] Acidification of the endosome is a frequent, if not universal, step in the endocytotic process.[3,4] It has been shown for a number of viruses (including retroviruses and human pathogens such as influenza A) that acidification triggers fusion of the viral membrane with the endosomal membrane, probably by a pH-induced conformational change in the viral membrane glycoprotein.[7] So-called lysosomotropic agents, weak bases which enter endosomes, have been shown to inhibit endosome acidification and thus block viral entry and infection[3,4,8-10] Two of these agents, chloroquine and amantadine, are widely used clinical drugs.

In the case of amantadine, although influenza A entry is blocked at clinically relevant concentrations, retrovirus entry is only inhibited at concentrations approximately two orders of magnitude higher. For chloroquine, clinically relevant plasma concentrations (100 to 300 ng per ml) are only three to ten times below the concentrations needed to cause 75% inhibition of viral entry in vitro.[8,11] Severe toxicity at higher doses precludes the use of substantially higher doses of chloroquine.[12] However, chloroquine is highly concentrated in certain tissues in vivo, notably in the cerebrospinal fluid (10 to 30 times plasma level), the reticuloendothelial system (6,000 times) and leukocytes (100 to 200 times).[13] This suggests that chloroquine could be effective in vivo, even though usual clinical plasma concentrations are somewhat below those needed for in vitro effects.

I suggest that amantadine, chloroquine and other antimalarials related to chloroquine[13-15] may be promising as rational agents for the prevention and early treatment of AIDS. Although their antiviral action of blocking pH-dependent viral entry into lymphocytes would be predicted to be a virustatic rather than virucidal action, they could still be of great potential value in preventing, slowing or arresting the relentless progress of the illness. Furthermore, the high concentrations attainable in cerebrospinal fluid suggest these agents might be especially valuable in treating central nervous system complications of AIDS where other drugs were excluded by the blood-brain barrier. Although evaluation of the anti-HIV effect of these drugs in vitro is a logical first step toward their clinical use, higher drug concentrations may be needed in vitro than in plasma due to the tissue concentrating effects described above. Since the effects of lysosomotropic agents can be additive in raising endosomal pH, the combination of these two drugs should be considered. Chloroquine has also been in wide use as a prophylactic antimalarial agent. Its relative lack of side effects, even during long-term administration, makes it a potentially attractive prophylactic agent for individuals known to be at high risk for AIDS. The low toxicity of these agents render them suitable as potential adjunctive treatments as well, in some form of combination chemotherapy.

I recommend that preclinical and clinical trials be carried out in research centers capable of measuring plasma drug levels, antibody titers and lymphocyte function in addition to clinical status so that a fair evaluation of the potential of these agents can be made.

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AIDS Vaccine Trial Volunteers Can Be Found

To the Editor: New California state legislation supportive of the development of an acquired immunodeficiency syndrome (AIDS) vaccine presumes that a sample of willing volunteers will submit to a vaccine trial. In terms of screening, subjects must be seronegative for the human immunodeficiency virus (HIV)—previously designated HTLV-III—at baseline, in a population where seroprevalence is increasing, and must be engaged in activity between baseline and follow-up likely to lead to viral infection. Injecting individuals with a vaccine, then expecting them to be engaged in behavior capable of exposure to HIV, poses ethical dilemmas. Testing persons for AIDS antibody before and after such a trial would require special assurances of confidentiality and may have psychological impact.[1] The question becomes, Who would volunteer?

Every six months since November 1983, the University of California, San Francisco, AIDS Behavioral Research

Project has gathered data on 676 San Francisco gay men's sexual practices and their willingness to take the AIDS antibody test.[2-4] In November 1985 we also surveyed respondents' willingness to participate in an AIDS vaccine trial. Of these respondents, 43% (292) reported that they would be willing to volunteer for such a trial, 14% (93) would not be willing and 43% (282) did not know whether they would volunteer. Only 22% (149) of the sample reported that they had been tested for antibodies to the AIDS virus, 72 of these persons reporting a negative status. There were 41 of these known antibody-negative persons who were willing to volunteer for a vaccine trial.

Vaccine trial volunteers were significantly more likely to have been tested for AIDS antibody (30%) than nonvolunteers (16%) or those who are unsure about volunteering (17%) ($\chi^2 = 16.2$, $df = 2$, $P = .00$). Nonvolunteers were more likely to have eliminated multiple-partner sexual activity capable of transmitting or receiving the AIDS virus (91%) than either volunteers (78%) or those unsure about volunteering (79%) ($\chi^2 = 8.0$, $df = 2$, $P = .02$).

Agreement with the following statements was surveyed of all respondents:

- I am concerned about the confidentiality of such a trial (88% agreed).
- I need to be reassured that the vaccine will not hurt me (92% agreed).
- Investigators should be sensitive to gay issues (97% agreed).
- I want to be paid to participate (19% agreed).
- I am willing to describe my sexual practices (95% agreed).
- I am likely to maintain the same type of sexual activity for the next year (93% agreed).
- I am likely to maintain the same number of sexual partners for the next year (89% agreed).
- I am willing to submit to antibody testing as part of this trial (77% agreed).
- I am willing to come to the University of California for the purpose of undergoing this trial (90% agreed).

Relationships between level of agreement with the above statements and overall willingness to volunteer were examined. One's decision to volunteer was related to being required to travel to the research site, reassurances about potential harm, desire for payment and willingness to take the antibody test. Concerns about confidentiality or about describing one's sexual practices did not relate to the decision for these men, who were already research participants. Those who expected to change their type of sexual practice were less likely to volunteer, and those who intended to reduce their number of sexual partners were more likely to say "no" or "I don't know" to the question of volunteering.

These results were drawn from a sample of highly cooperative gay men who have stayed with this study for several waves of data collection, thus they may not be representative of gay men in general. However, a sizable number of seronegative men from this group are willing to volunteer, given the proper assurances. More are willing whose antibody statuses have not yet been determined. A recruitment procedure could be devised that would find similarly cooperative men. Some amount of high-risk activity persisted in persons who were willing to volunteer for the trial in November 1985. The small overall percentage of the sample engaged in high-risk sex at that time (20%) reflects the successes in this city of public health education efforts. However, from the standpoint of vaccine trial screening criteria, more high-risk sex may need to be occurring in the test population. Also, given the high, stable seroprevalence of the AIDS virus in San Francisco,[5] other urban sites with lower AIDS virus seroprevalence may be better suited to a trial by the time investigators are ready to proceed.

The ethical issues associated with administering an untried vaccine to persons engaged in high-risk sex without discouraging this sexual activity are not addressed by this study. However, these results do suggest that problems in sampling for such a trial are not insurmountable, if the investigators are able to provide reassurances of safety and convenience to potential volunteers.

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Concept of Cognitive Versus Procedural

TO THE EDITOR: I have just read "Changing Physician Payment for Medicare Patients"[1] in the November issue.

It is time to call a halt to the spread of a practice that is inaccurate, misleading, divisive and insulting to a large part of the medical community. I refer to the attempt to divide physicians' services, or even the physicians themselves, into "cognitive" and "procedural."

If the elders of the American Society of Internal Medicine want to be reimbursed at a higher level, more power to them. But there is a reason why one consults a general surgeon to help evaluate atypical abdominal pain, or a vascular surgeon to unravel the causes of a swollen or painful leg. The repair of a thoracoabdominal aortic aneurysm or the relief of an intestinal obstruction due to metastatic colon cancer requires experience, knowledge, judgment and wisdom on the part of the surgeon.

More than ever, physicians need to hang together, or we shall most assuredly hang separately. Let's banish this "cognitive/procedural" malarkey from all respectable medical publications.

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Greater Awareness of Sulfite Allergy Needed

To the Editor: The number of complaints of sulfite allergy has grown from 50 to more than 300 at present, with the news media reporting some fatalities said to be related to sulfites.[1] The previous generally regarded as safe (GRAS) classification by the Food and Drug Administration (FDA) has changed to a requirement for labels disclosing the presence of sulfites in packaged fruits and vegetables,[2] and state health departments are currently providing test kits for their district health departments (March 1985 news release, Idaho Department of Health, Fritz Dixon, MD) to test for the presence of sulfites in retail stores to assure compliance with the regulations. The FDA step and further public awareness of the presence of sulfites and their allergy-causing potential are important to help the 1 million or more people who may have the problem to become aware of the potentially fatal condition.

Reports of Cases

We present two cases that illustrate the need for public awareness and a high index of physicians' suspicion to help these undiagnosed patients with their allergic reactions.

A 45-year-old woman had a history of asthma and allergies to shellfish, iodine and penicillin, with allergic reactions manifested by hives and asthma over a five-year period. The episodes were initially seasonal and related to exposure to previously identified allergens. She had also noted, however, increasing problems with hives, flushing and bronchospasm requiring emergency room treatment and subsequent hospital admission; these occurred unpredictably, with growing frequency and mostly following meals at restaurants. Allergists were involved in her care and evaluation. Allergy testing failed to disclose any specific allergens.

On two occasions the patient saw national news programs on bisulfite allergy. She notified us of her suspicion and avoided bisulfites. Since then she has had only rare occurrences of reactions and these were related to inadvertent bisulfite exposure: Once she ate lamb that had been unintentionally treated with bisulfite and another time food prepared in oil previously used to prepare bisulfite-treated food.

The second patient, also a 45-year-old woman, had a several months' history of increasing hives, dyspnea, a tight feeling in the throat, nausea and headache. She had been evaluated by dermatologists and an allergist, with no specific diagnosis or specific allergens identified. We considered the possibility of food allergy and an elimination diet was tried. When the patient was consuming only fresh vegetables she noted that she still had the reactions. Because of the previous patient's history, we considered bisulfite sensitivity. The patient meticulously avoided all bisulfites and has been clinically free of symptoms since. The store where she previously had bought fresh vegetables used bisulfite spray, she later discovered.

Discussion

These two cases illustrate the importance of public awareness and of a high index of suspicion by physicians in diagnosing sulfite allergies. Many perplexing cases of allergy symptoms with no specific diagnosis may be related to bisulfites. At present, there are no specific tests, other than challenge with bisulfites, to make a diagnosis.[3] Also, there have been no consistent predisposing patient profiles that would allow one to determine who may be at greater risk for bisulfite allergy.[4]

The current policy of the FDA needs to be expanded to cover products that have been previously treated with bisulfites. In addition, a greater index of suspicion by clinicians would aid in diagnosing bisulfite allergy—which can cause a variety of allergic manifestations including anaphylaxis—and help many patients avoid needless medical expense, morbidity and possibly mortality from this ubiquitous substance.

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Physician Production and Influx

To the Editor: I am writing regarding the editorial "Needed Clout for Patient Advocacy"[1] in the November 1986 issue.

It is a rare thing to see acknowledgment from the medical hierarchy, as in your editorial, that our system of health care "has become dominated by economic factors." 'Tis true. 'Tis true. And yet this acknowledgment has been as tightly held as the spare, infrequent acknowledgment that there might be excessive numbers of physicians in the United States or that such supernumerary physicians might have something to do with this grave wounding of our profession and its mission. In fact it is the root cause. It is past time for these acknowledgments and for concerted efforts to gain control of physician production and influx.

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REFERENCE

1. Watts MSM: Needed clout for patient advocacy (Editorial). West J Med 1986 Nov; 145:685

Correction: Computer Programs for Physicians

To the Editor: Our article "Bringing the Medical Literature to Physicians—Self-Service Computerized Bibliographic Retrieval"[1] contains two errors in the last paragraph on page 853. In the following sentences, the words in brackets indicate what should be deleted: "In addition to the National Library of Medicine, Bibliographic Retrieval Services (BRS) [*not* /Saunders Colleague] and Dialog also provide computer programs. . . . More recently, the National Library of Medicine, Mead Data Central, BRS Colleague [*not* /Saunders] and Dialog have begun to offer more user friendly approaches to the MEDLINE data base." The first "Saunders" seems to have been mistakenly added during the editing process. In the second case, "Saunders" recently has been deleted from the name of the service.

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Radiologic Case

Double Vision in a Patient With Lymphoma

TODD KENNELL, *Tucson;* JONATHAN M. LEVY, MD, *and* CARY J. STEGMAN, MD, *Scottsdale, Arizona*

A 40-year-old woman complained of double vision. She had recently been found to have abdominal lymphoma and was under treatment. A computed tomographic (CT) scan of her orbits is shown in Figure 1.

What is the abnormality?

How would you treat this woman?

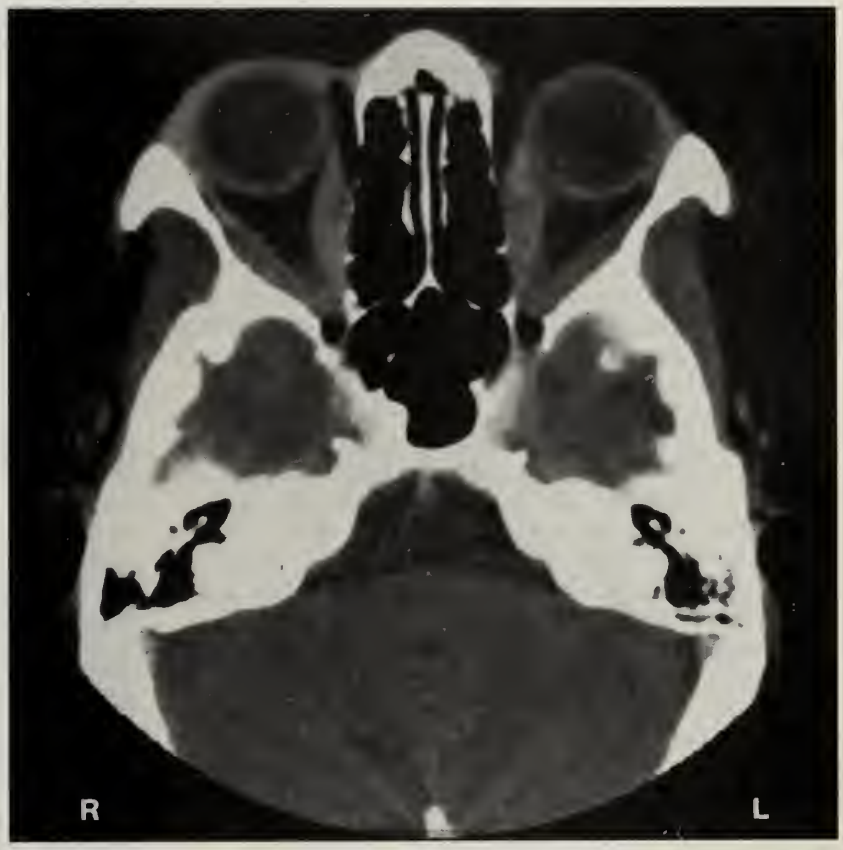

Figure 1.—A computed tomographic scan through the orbits of a 40-year-old woman.

(Kennell T, Levy JM, Stegman CJ: Double vision in a patient with lymphoma [Radiologic Case]. West J Med 1987 Feb; 146:241-242)

From the University of Arizona College of Medicine, Tucson (Mr Kennell), and the Department of Diagnostic Radiology, Scottsdale Memorial Hospital, Scottsdale, Arizona (Drs Levy and Stegman).

Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

ANSWER: Extraocular muscle hypertrophy due to hyperthyroidism (Graves' disease)

When the patient's CT scan (Figure 1) is compared with a normal study (Figure 2), the smooth, symmetric enlargement of the medial and lateral rectus muscles is obvious. There is no nodularity of the muscle bodies, and no orbital mass is seen. The tendons at their attachments to the globes are of normal size. These findings are strongly indicative of Graves' disease, even in a patient with lymphoma.

In hyperthyroidism, the extraocular muscles undergo an inflammatory reaction, which leads to fusiform, smooth expansion of the muscle bellies. The hypertrophy may affect one or a group of muscles selectively, but it is usually symmetric and bilateral. Changes in other orbital structures frequently occur concurrently. Increased fat volume leads to prolapse of the orbital septum. Lacrimal glands may swell, and if apical enlargement is severe, the optic nerve and superior ophthalmic vein become distended.

Graves' disease is by far the most common cause of extraocular muscle enlargement. Less common disorders producing this finding include myositic pseudotumor, arterial-venous fistula, acromegaly, trauma and tumors invading the muscles. Myositic pseudotumor produces smooth and often bilateral muscle enlargement and therefore is an important differential consideration. Both the muscles and their tendons usually swell in this process, however, whereas in Graves' disease the tendons remain of normal size (Figure 1). The other differential diagnoses listed do not usually produce the bilateral and symmetric changes seen in hyperthyroidism. Tumors, including lymphoma, produce nodular rather than smooth enlargement of the muscles and only very rarely produce symmetric enlargement.

Treatment of Graves' ophthalmopathy is most successful after a euthyroid state has been established. Hyperthyroidism associated with Graves' disease can be treated with radioiodine administration, antithyroid drugs or surgical ablation, with radioiodine being used most often at present. After amelioration of the hyperthyroidism, prednisone is given systemically in an attempt to reverse the muscle swelling. Focused linear-beam irradiation and surgical decompression have also been used for this purpose.

Figure 1.—A computed tomographic scan through the orbits of a 40-year-old woman with Graves' disease.

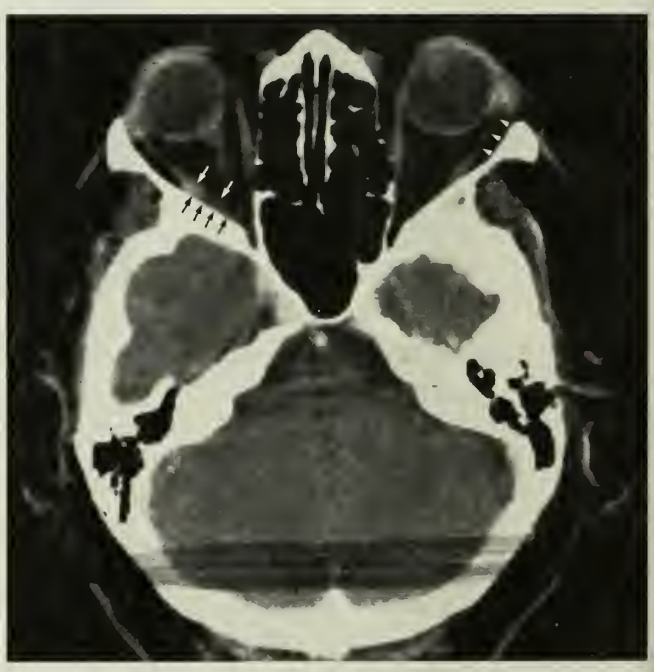

Figure 2.—A computed tomographic scan of the orbits in a normal patient. Note the thin muscle bundles **(black and white arrows)** and the normal tendons **(arrowheads).** Muscles in Figure 1 are enlarged, whereas tendons are normal.

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Factors Associated With Pedestrian-Vehicle Collision Injuries and Fatalities

BETH A. MUELLER, DrPH; FREDERICK P. RIVARA, MD, MPH, *and* ABRAHAM B. BERGMAN, MD, *Seattle*

Data from Washington State police records of pedestrian-vehicle collisions were used to tabulate injury and fatality rates for 1981 to 1983 and to investigate event characteristics associated with the occurrence of fatalities. Case-fatality rates are seen to be relatively higher when there is decreased visibility due to fog, lack of lighting or dark color of pedestrian clothing. Fatality rates from death certificate data for the same time period were compared with the police-reported rates. For children younger than 5 years, fewer cases of pedestrian death are reported by police than by death certificate, because a large proportion of fatal injuries (27%) is not traffic related or occurs at home (46%) in the garage or driveway.

(Mueller BA, Rivara FP, Bergman AB: Factors associated with pedestrian-vehicle collision injuries and fatalities. West J Med 1987 Feb; 146:243-245)

More than 8,000 people die each year in the United States as a result of pedestrian-motor vehicle collisions. In urban areas, pedestrian injuries are the most common cause of injury death among children 5 to 9 years of age.[1] Prevention strategies relying on behavior change have had, at best, only modest success.[2-5] Environmental factors, however, including aspects of vehicle design[6,7] and road and signal construction,[8,9] have been shown to have an impact on injury occurrence. There is a need for studies that examine other factors in the environment which may decrease the toll of pedestrian injuries and fatalities.

The purpose of the present analysis is threefold:

1. To measure the magnitude of this problem in Washington State by tabulating injury and fatality rates as derived from two sources—police records and death certificates.
2. To identify environmental factors associated with increased case-fatality rates by using the collison-incident information collected in police reports.
3. To compare these police-reported fatality rates with those derived from death certificate data from the same time period to investigate the nature of underreporting in police data.

Methods

In the present study we used data from two sources for the three-year period from 1981 to 1983. Washington State Department of Transportation records of all police-reported motor vehicle collisions where there was pedestrian involvement were used to compute annual injury and death rates and to evaluate various event characteristics with respect to the occurrence of pedestrian-vehicle incidents (PVIs). Reporting of all motor vehicle collisions by state and local police and sheriff's departments is required by the Department of Transportation; therefore, these data (and similar data from other states) are frequently used as a population-based indicator of motor vehicle-related injury occurrence. The second source of the data was the Department of Vital Statistics death certificate file containing the records of all deaths in Washington State coded with *International Classification of Diseases* ICD-E codes 814 to 825 (pedestrian-vehicle deaths). Death certificate data were assumed to be the best available indicator that a PVI-related death had occurred and were used as the standard against which police-reported PVI fatalities were compared. Underreporting of motor vehicle injuries by police data has previously been shown.[10,11] Our concern in the present study was to compare these two sources in an effort to identify subgroups where systematic underreporting of pedestrian-vehicle injuries may be a problem.

To allow comparison of death rates computed from these two sources, the data were restricted to those fatal PVIs occurring in Washington State during 1981 to 1983 to a Washington State resident only. Persons with records in the death certificate data who died of injuries due to a PVI that occurred in another state and who were brought to Washington for hospital care were not included. Average annual injury and death rates were computed using the 1980 US census figures for the state as denominator and assuming a stable population base during the study period.

Results

A total of 5,065 pedestrian-vehicle collisions involving Washington residents were reported by police during the three-year interval from 1981 to 1983 in which 5,248 pedestrians were involved. PVIs in which more than one pedestrian was injured were less than 4% of the total. The number of pedestrian-vehicle collisions is compared in Table 1 with the number of nonpedestrian-motor vehicle collisions occurring during the same interval. PVIs are a less frequent but much more lethal occurrence as indicated by comparing the proportion of fatal events for PVIs (6%) to that for motor vehicle

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collisions in which a pedestrian was not involved (0.6%). In addition, virtually all PVIs reported involved an injury, whereas less than 40% of the other motor vehicle collisions involved a reported injury.

The annual rate of police-reported PVI injuries was 40.0 per 100,000 population (Table 2). The annual death rate using these data is 2.4 per 100,000. Age-specific rates vary greatly. Children and adolescents 19 years of age and younger were seen to be at highest risk of pedestrian injury, while the elderly and the very young are at greatest risk for dying. The case-fatality rate is high for young children, decreases for children 5 to 14 years of age and then rises again for children older than 15 years, a finding that is unexplained, as children in these age groups should be better able to survive trauma than those in the older age groups.

Using death certificate data, it was possible to compare the risks of pedestrian fatality among different racial groups. Most nonwhite groups were found to have higher death rates due to PVI than did whites. No PVI fatalities were seen for Asian groups including Japanese, Chinese, Korean, Asian Indian, Vietnamese and Hawaiian. Death rates per 100,000 population for other racial groups were 2.4 for whites, 3.8 for blacks, 5.6 for "other" and 14.8 for Native Americans (including American Indian, Aleut and Eskimo).

Selected event characteristics and location of PVI were evaluated using Department of Transportation data (Table 3). Limited visibility due to fog or lack of streetlights was associated with an increased case-fatality rate to a greater extent than were adverse road conditions due to snow and ice. That pedestrian visibility is a key factor is also shown by the lower case-fatality rate seen when light or bright colors were worn by the pedestrian. The location of a pedestrian when struck was also examined. Approximately a third of all pedestrians were injured while in marked crosswalks.

Events were coded in the Department of Transportation data as having occurred in an urban area if they were either in or adjacent to a municipality of at least 5,000 population. Using this classification, 624 of the total 5,248 pedestrians, or 12%, were injured in rural areas. The case-fatality rate for rural pedestrians, however, at 14.3% was much higher than that of 4.4% for urban pedestrians.

Although the death rates calculated using Department of Transportation data are generally similar to those from death certificate data (Table 2), deaths to children younger than 5 years appear to be underreported in the police data. Death rates from death certificate data indicate that the very young are at higher risk for pedestrian injury fatality than any other age group, with the exception of the elderly. Analysis of the death certificate data indicates that fatal pedestrian-vehicle injuries to children younger than 5 years may differ from those to older children and adults. A large proportion (46%) of these deaths to children younger than 5 occurs at home, presumably in the driveway or garage, and 27% are coded with the ICD-9 codes for nontraffic pedestrian-vehicle collision as cause of death.

Discussion

Underreporting of nonfatal motor vehicle injuries by police records has previously been shown.[11] In the present analysis, we find that, even for fatal injuries, police reports are incomplete, and we have determined the nature of the underreporting and an age group where underreporting is most common. Studies of pedestrian injuries that rely exclusively on police-reported data are likely to systematically exclude nontraffic incidents occurring in driveways, garages or apartment building parking areas where the victim is younger than 5 years.[12,13] Most of the nontraffic fatalities that occurred in Washington during the study period (59%) were to children younger than 5 years. Of all fatalities that occurred at home, 68% were to this age group. This suggests that a different focus is necessary to bring about a reduction in pedestrian fatalities to young children, requiring environmental changes in the home as well as on the street.

TABLE 1.—*Injury and Fatal Pedestrian-Vehicle and Other Motor Vehicle Collisions in Washington State—1981-1983**

Collision Category	Collisions 1981-1983, No.	Nonfatal Injury, %	Fatal, %
Pedestrian	5,065	93.9	6.0
Nonpedestrian†	314,169	36.7	0.6
All motor vehicles	319,234	37.6	0.7

*Source: Data Summary and Analysis of 1983 Traffic Collisions Washington State, US Department of Transportation.
†Includes 10,857 motorcycles and 3,369 pedalcycle collisions.

TABLE 2.—*Average Annual Age-Specific Pedestrian-Vehicle Injury and Death Rates* in Washington State—1981-1983*

Age Group, Yr	Police Reported†			Death Certificate Deaths
	Injuries	Deaths	Case-Fatality Rate, %	
< 5	25.6	1.5	5.6	4.0
5-9	76.4	2.3	2.9	2.6
10-14	65.0	1.6	2.3	1.8
15-19	53.6	3.2	5.6	2.7
20-24	39.6	2.1	5.0	2.1
25-29	32.7	1.7	5.0	1.7
30-44	26.1	1.8	6.4	1.9
45-64	20.9	1.8	8.1	2.1
65+	37.8	5.9	12.9	6.6
All ages	40.0	2.4	5.6	2.7

*Per 100,000 population based on 1980 US census figures.
†Washington State Department of Transportation.

TABLE 3.—*Police-Reported Fatal Pedestrian-Vehicle Incidents by Selected Event Characteristics, N = 5,248*

Characteristics	Injuries, No.	Fatal, %
Road surface		
Dry	3,621	5.7
Wet	1,471	5.4
Snow	81	4.9
Ice	75	4.0
Visibility-weather*		
Clear	4,011	5.7
Rain	1,109	5.1
Snow	74	2.7
Fog	52	7.7
Visibility-light		
Daylight	3,123	3.2
Dawn/dusk	225	4.9
Dark and streetlights	1,367	6.9
Dark—no streetlights	533	16.7
Pedestrian clothing color†		
Light/reflective color	798	3.4
Mixed colors	2,148	5.4
Dark color(s)	1,613	8.2

*Weather unknown for 2 cases.
†Clothing color unknown for 689 cases.

The rate of injuries and the case-fatality rates varied substantially with a number of factors. High rates of pedestrian injury for the very young and the elderly have been noted in previous studies.[14-16] The high case-fatality rates seen here for adolescents and young adults, however, have not been previously commented on. Biologically, the adolescent and young adult populations overall have the greatest capacity to survive trauma, compared with any other age group.[17,18] The limitations of the data do not allow us to determine if the injuries in this group are more severe or if other factors are at work to increase their risk of a fatal outcome. Increased alcohol use in this age group may be a factor; it is unclear, however, whether or not alcohol intoxication is associated with increased mortality from motor vehicle injuries.[19,20] Data limitations precluded our analysis of alcohol use among the pedestrians. The increased case-fatality rate in young adults seen here warrants further study.

The differences in race-specific pedestrian fatality rates were also pronounced. The absence of deaths in Asians is surprising, given the fact that they constitute 4% of the population in the state. Previous work has indicated that most Asian groups have relatively lower unintentional injury rates than other racial groups.[1] The possibility of miscoding of race in the data, however, cannot be ruled out.

The striking increase in fatal outcome for pedestrians injured in rural areas compared with urban areas has also been noted by others[1] and has usually been ascribed to faster speeds of motor vehicles on rural roads. Other factors that might increase the risk of a fatal outcome in rural areas include a greater delay in arrival of emergency medical services,[21] the level of prehospital care received[22,23] and the unavailability of intensive trauma care in small, rural hospitals.[18] All of these factors have important implications for prevention.

The site of the pedestrian-motor vehicle collisions appears to play a role in causing injury and deserves further investigation. Although the fact that a third of pedestrian injuries occur in crosswalks does, in part, reflect exposure, there is a need to reexamine the effectiveness of crosswalks in preventing pedestrian injury.[24,25] In crosswalks, the presence of a pedestrian *in the street* is the signal for a driver to stop; an unseen pedestrian may have a false sense of security by being in a crosswalk. This issue of exposure of injured and noninjured pedestrians in crosswalks needs to be examined further.

The toll due to pedestrian-vehicle collisions can be reduced. Results of this analysis suggest that environmental changes such as improving street lighting and separating children's play areas from garage and driveway (or creating alternative play areas) may have an impact. It is possible that speed bumps or other engineering changes may reduce the number of injuries that occur in crosswalks. In rural areas, resultant mortality may be decreased by factors influenced by emergency medical systems and emergency services at hospitals. The issue of underreporting of injuries in data routinely used for injury-prevention studies is a cause for concern and lends support to the need for a uniform injury surveillance system. At present, injury researchers must continually be aware of existing gaps in commonly used reporting systems.

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Special Article

Rising Malpractice Premiums and Obstetric Practice Patterns

The Impact on Family Physicians in Washington State

ROGER A. ROSENBLATT, MD, MPH, *and* CRAIG L. WRIGHT, *Seattle*

All 853 active members of the Washington Academy of Family Practice were surveyed in the summer of 1985 to determine the impact of rising malpractice premiums on patterns of obstetric practice. Of the 685 physicians who responded, 61% are currently practicing obstetrics. The median number of deliveries per year was 29, with a range of 1 to 130 deliveries per physician. Younger physicians, rural physicians and those in group practice were more likely to practice obstetrics than older, urban physicians in solo practice. Of the 266 respondents not currently practicing obstetrics, 77% had discontinued obstetric practice within the past five years—half because of issues related to professional liability. Of those practicing obstetrics, 50% stated that they would cease obstetric practice if malpractice premiums rose to $12,000.

(Rosenblatt RA, Wright CL: Rising malpractice premiums and obstetric practice patterns—The impact on family physicians in Washington State. West J Med 1987 Feb; 146:246-248)

The medical malpractice issue has emerged as one of the most powerful forces shaping the practice of medicine in the United States in the 1980s. The impact of the medical malpractice crisis has been most pervasive in the practice of obstetrics.[1] Obstetric practice is provided for the most part by obstetrician-gynecologists and general and family practitioners, and both groups have had to redefine the scope and content of their obstetric practice in the wake of a growing number of suits and large increases in malpractice premiums. The full impact of these changes on the future of obstetric practice is unclear.

Obstetric practice is a discretionary part of a family physician's clinical repertoire. The proportion of family physicians actively practicing obstetrics varies greatly by region of the country, urban or rural location and physician age.[2] Because malpractice premiums are much higher for family physicians who include obstetrics in their practices, the differential cost must be spread over a relatively small number of patients. Thus, rising malpractice premiums may make it economically infeasible for family physicians to continue obstetrics.

This study was designed to assess the extent to which proposed increases in malpractice premiums for family physicians in Washington State were likely to affect their future obstetric practice. Because family physicians represent an important clinical source of obstetric care in this state, the potential loss of a large number of physicians might sharply limit access to care for a large group of patients. In addition, because family physicians are the predominant source of medical manpower in rural areas, patients in these locations might be forced to travel long distances for obstetric care or to forego traditional obstetric care altogether.[3]

Methods

A questionnaire was sent to all 853 members of the Washington Academy of Family Physicians, a group whose membership includes the majority of general and family practitioners in the state. The one-page survey asked questions about the organization of a physician's practice, the amount of effort devoted to obstetric care and a number of specific queries about the impact—past, present and future—of malpractice premiums on the extent of obstetric services offered. The questionnaire was pilot tested before distribution, and two mailings were sent to ensure an adequate response. In all, 685 physicians returned a properly completed survey, yielding a response rate of 80%.

Results

Characteristics of Respondents

Of the 685 respondents, 85% were board certified in family medicine. The median number of years they had been in practice was 13. About 36% of the respondents had completed residency training in family medicine.

As Table 1 shows, 82% of the respondents are in private practice, with group practice the most popular mode. About 14% are in salaried practice, employed either by health maintenance organizations or in hospital settings such as emergency rooms. Of the sample, 26% are in nonmetropolitan

From the Department of Family Medicine, University of Washington School of Medicine, Seattle. Mr Wright was a second-year medical student at the University of Washington when this study was done.

This study was supported by the W. K. Kellogg Foundation. We acknowledge the cooperation and assistance of the Washington Academy of Family Physicians, the Washington State Medical Association and the Washington Physicians Insurance Exchange and Association.

Reprint requests to Roger A. Rosenblatt, MD, MPH, Professor and Vice Chair, Department of Family Medicine, Research Section HQ-30, University of Washington School of Medicine, Seattle, WA 98195.

areas as defined by the US Census, with the largest number of practitioners working in large cities.

A total of 419 of the respondents—61% of the sample—currently are directly involved in providing obstetric care. Younger physicians, rural physicians and those in group practice were significantly more likely to practice obstetrics than older, urban or solo practitioners. Although 71% of female physicians practice obstetrics as compared with 60% of male physicians, this difference is probably due to the fact that the female physicians in this study are younger than their male counterparts.

As shown in Figure 1, there are large differences in the obstetric load of family physicians in Washington State. The median number of deliveries is 29 annually, with a range from 1 per year to 130 per year. These differences in obstetric volume seem to be related more to individual differences among physicians rather than any systematic differences due to practice location, physician age or gender, board certification or residency training or the organization of the practice. No specific subgroup of physicians practicing obstetrics could be identified that had either a very high or a very low volume of deliveries.

Impact of Malpractice Premiums on Obstetric Practice

In all, 198 of the respondents reported that they had stopped practicing obstetrics during the past five years, representing 29% of all respondents and 74% of the 266 respondents not currently practicing obstetrics. An additional 126 physicians—18% of the respondents—reported a decrease in obstetric volume during the same period. About half of those who had stopped or decreased their obstetric practice cited professional liability issues as the primary cause—both the reality of increased premiums and the fear of future malpractice suits. The balance of those with curtailed obstetric involvement gave a variety of reasons for the change in practice patterns, with the leading factor being the personal inconvenience and practice disruption caused by obstetric practice. Table 2 contrasts the characteristics of physicians who have maintained their obstetric practice at past levels during the past five-year period with those groups who had either curtailed practice or ceased obstetrics entirely. As noted earlier, a cluster of interrelated characteristics is associated with the decision to continue practicing obstetrics: relative youth—as measured by the amount of time in practice; residency training and board certification, and group practice.

Future Trends in Obstetric Practice

The 419 respondents who were currently practicing obstetrics were asked to predict how a rise in malpractice premiums would affect their practices. Exactly half responded that they would probably cease practicing obstetrics in response to further premium rises. To quantify that expressed intention, we specified specific premium levels ranging from $8,000 per year to $32,000 per year and asked the respondents to indicate the level at which they would seriously consider not offering obstetric care. As can be seen in Figure 2, the effect is linear, with most respondents willing to tolerate premiums of $8,000 and virtually none willing to continue obstetrics if premiums rose to $32,000, the level for obstetrician-gynecologists prevailing at the time of the survey. At $12,000 per year for occurrence malpractice insurance, about half of the respondents predict they would cease obstetric practice.

Discussion

The rapid increase in malpractice premiums is being driven by two major factors: an increase in the number of claims filed and an increase in the size of malpractice awards. In Washington State, 6 claims were filed per 100 practicing physicians in 1971. The incidence of new claims had increased to 15 per 100 physicians in 1981 and to 21 by 1984 ("Medical Malpractice," *Seattle Post-Intelligencer,* September 1, 1985, p F-4). During the ten-year period from 1975 to 1984, the size of the average award has nearly quadrupled, rising from $50,000 in 1975 to nearly $200,000 in 1984. Not

TABLE 1.—*Characteristics of Survey Respondents (N=685)*

Practice Characteristics	*Number*	*Percent of Total*
Currently practicing obstetrics	419	61
Private group practice	317	46
Private solo practice	243	36
Health maintenance organization	69	10
Hospital-based	28	4
Other	28	4
Totals	685	100
≤15 years in practice	406	59
>15 years in practice	279	41
Totals	685	100
Practice Location		
Large metropolitan area	396	58
Small metropolitan area	112	16
Rural	177	26
Totals	685	100

TABLE 2.—*Differences Among Physicians Who Have Maintained, Decreased or Stopped Obstetric Practice During the Past 5 Years (N=605)**

	Maintained (N=281)	*Decreased (N=126)*	*Stopped (N=198)*
Percent women	16	9	8
Average years in practice	12	18	23
Percent in solo practice	25	38	50
Percent board certified	96	84	70
Percent finished family practice residency	63	30	19
Percent in rural areas	29	42	20

*80 questionnaires were deleted because of incomplete or inconsistent responses to this question.

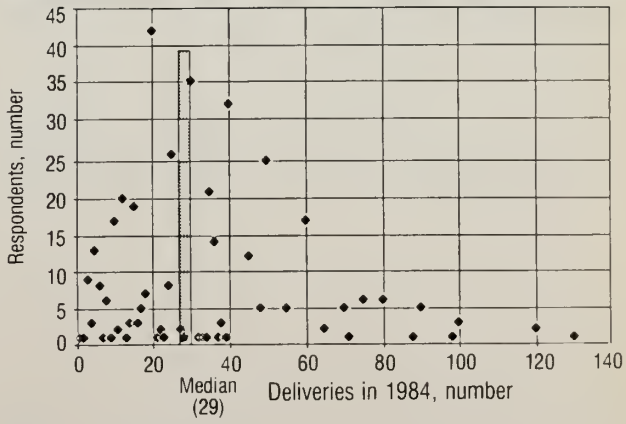

Figure 1.—Number of deliveries in past year by family physicians in Washington State who practice obstetrics (N = 419).

surprisingly, the cost of malpractice insurance has increased commensurately.

Obstetric care represents a segment of medical practice that is extremely sensitive to changing patterns of professional liability. More than 3 million births occur annually in the United States. Despite rapid advances in perinatal medicine, not every pregnancy results in a healthy baby. About 1 in every 100 babies will die during the perinatal period and an even larger number will experience significant morbidity, some of which will entail lifelong sequelae. Obstetrics will never be a risk-free endeavor, for either a mother, child or physician.

Because injuries to infants tend to be severe and of long duration, the awards in malpractice cases have been very large. In one study, the average award in cases involving injuries to infants was more than $1,400,000, whereas the average award for all other categories was less than $200,000.[4] As a consequence, malpractice premiums have risen particularly rapidly for physicians practicing in this area.

Obstetrics is a discretionary part of the clinical repertoire of family physicians. In this study, the average respondent with an active obstetric practice delivered 29 babies last year. In 1986 the malpractice premiums for family physicians who practiced obstetrics and were insured by the largest carrier in the state was $13,511; by comparison, the premium for family physicians without obstetrics was $4,324. Thus, the incremental insurance amounted to $317 per child delivered for a typical practitioner. Adding to the fiscal burden for physicians is the shift in most cases from occurrence to claims-made insurance, which requires physicians to remain in practice for at least ten years or purchase costly "tails" when they retire or move to another practice setting.

This study shows that the rapid increase in premiums has had, and will continue to have, a significant impact on practice patterns. If physicians' behavior mirrors their intentions, more than half of all family physicians in the state of Washington will cease practicing obstetrics during this coming year. This has significant ramifications not only for the future of family medicine as a clinical discipline, but will inevitably make it more difficult for important segments of the population to obtain obstetric care near where they live.

As this study shows, about 25% of family physicians practice in rural locations, settings in which they are frequently the only physicians providing obstetric care. Because it is very difficult for a physician to maintain an obstetric practice without some sort of coverage arrangement with colleagues, the loss of one or two physicians in many small communities may make future obstetric practice untenable even for those who wish to continue with this activity. As family physicians forego obstetric practice, patients will be forced to travel to other towns to receive their care. Provocative evidence is beginning to emerge that providing technologically intensive obstetric practice to a low-risk population may actually lead to poorer perinatal outcome, to say nothing of the increased cost and inconvenience shouldered by the women and families who can no longer obtain care in their communities.[5]

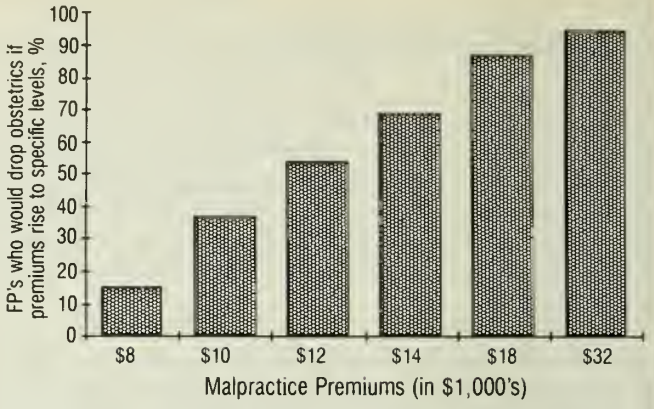

Figure 2.—Impact of specific malpractice premiums on obstetric practice of family physicians (FPs).

There is no simple solution to this problem. It is clear from this survey that obstetric practice has remained an important part of family practice to date. It appears, however, that rising malpractice premiums will have a profound impact on the practice patterns of family physicians. If premiums rise as predicted, obstetrics will be practiced by a minority of family physicians. Perhaps more important, this change is likely to make it more difficult and more expensive for women to obtain obstetric care, and women living in small communities may be forced to travel to other towns for what has been considered a rather fundamental component of primary medical care.

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Information

Chronic Mononucleosis in Adults

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THE EPSTEIN-BARR VIRUS (EBV) is a ubiquitous organism that infects 85% of the population by the age of 30. A common manifestation of this virus is acute infectious mononucleosis, which characteristically afflicts persons in their teens and early 20s, and is often euphemistically referred to as "the kissing disease" because of its presumptive mode of transmission. The characteristic three-week to three-month period of fatigue, lassitude, sore throat, lymphadenopathy and low-grade fever is well known to most physicians. Positive antigen-specific antibody tests and hematologic findings confirm the diagnosis.

Over the past five to ten years, a number of cases of an EBV-related syndrome akin to mononucleosis but occurring in adults has been reported, but with some significant differences. Although the disease has many clinical similarities to the adolescent form of infectious mononucleosis, its most devastating characteristic is its chronicity. Victims may suffer symptoms for periods ranging from six months to seven years. Other differences are the frequent absence of prominent lymphadenopathy and the evanescence of the laboratory tests. Characteristically, those afflicted are high-energy types, often middle-aged, with busy lifestyles.

An initial period of intense prostration accompanied by sore throat, low-grade fever and often with severe myalgia is followed by a protracted recovery period whose hallmark is a feeling of denervation. In the initial phase, an otolaryngologist/head and neck surgeon may be consulted, not only because of the pharyngitis and adenopathy but because many patients have intense paranasal sinus pain, usually involving the maxillary sinuses. Sinus x-ray films are normal, and antral irrigations, if done, are nonproductive. The pharynx is usually slightly reddened and granular in appearance, with erythema and swelling of the lateral pharyngeal bands. The characteristic white membrane and hypertrophic appearance of the tonsils seen in the adolescent form are commonly absent. The pharyngeal symptoms are like a barometer, often heralding a worsening of the disease during periods of fatigue or just before relapse. Another characteristic feature of the syndrome is this latter proclivity to relapse, which tends to follow periods of excess physical activity or mental stress or can occasionally occur spontaneously without a precipitating cause. During these times, lassitude, fatigue and an overall sense of weakness are pathognomonic. Facial, pharyngeal and muscular pain present in the initial-stage return. Depression almost invariably accompanies this disorder and is of both the endogenous and exogenous types. The EBV, similar to the hepatitis viruses, has a direct effect on the limbic system. This, coupled with the frustration and boredom brought about by enforced bed rest, deprivation from normal work, exercise and family activities, a sense of life passing one by and the frequent lack of understanding by family, friends and especially health care professionals who often pass the patient off as a "crock," often produces a profound depression that occasionally renders a patient suicidal. Laboratory tests are often of little value. If a blood specimen is drawn early in the course of the disease, the Mono spot test may be positive and the characteristic "butterfly lymphocytes" may be found. Because patients often present late due to misinterpreting early manifestations as "the flu," these tests are usually negative. An elevated EBV antibody titer is commonly seen and often parallels the clinical course of the disease, being worse during relapses. Even this test is not always reliable, however, and false-negatives are not uncommon. A transient mild elevation of the antinuclear antibody titer is occasionally seen.

The disease is self-limiting. Patients slowly recover, often in a series of plateaus with occasional exacerbations lasting from five days to three months. The time course for complete recovery varies, but is often from two to four years in duration. Nonnarcotic analgesics help relieve pain. One of these, sulindac, which is effective for various arthritic conditions, frequently reduces the effects of the disease. In clinical trials, antiviral agents, such as acyclovir, have had no effect. The use of steroids early in the course of the illness may abort the process, but their use is controversial and not always beneficial. Antidepressants such as amitriptyline hydrochloride, usually in low doses (15 to 50 mg), are very effective in relieving depressive symptoms.

(Donald PJ: Chronic mononucleosis in adults. West J Med 1987 Feb; 146:249)

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GENERAL REFERENCES

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

PHYSICIAN-SPONSORED HMO DEVELOPMENT—Prepared by Eric R. Wagner and Valerie J. Hackenberg for the American Society of Internal Medicine. ASIM, 1101 Vermont Ave, NW, Suite 500, Washington, DC 20005, 1986. 63 pages, $10 (ASIM members), $15 (nonmembers).

This book provides a brief guideline for use by any group of physicians considering establishing a nonstaff model health maintenance organization (HMO). Its essence is contained in three primary chapters: "Determining the Feasibility of HMO Development," "Organizational Development" and "Development Activities."

Each chapter contains brief descriptions of the actions necessary before proceeding to the next stage of HMO development. For example, organizing physicians, selecting a consultant and assessing the market and financial implications are key elements in feasibility determination. The "Organizational Development" chapter includes guides for selecting legal counsel and establishing governing and management structures. The most lengthy section, "Development Activities," outlines the myriad activities involved in making an HMO operational—for example, capital formation, legal and regulatory compliance, provider recruitment and selection credentialing, utilization management, quality assurance and compensation. Each chapter concludes with a series of questions that are basic to the completion of the tasks outlined in the previous discussion.

The book is very useful in that it sets forth both the steps and the timetables involved in establishing an HMO. For physicians with limited knowledge of HMO development, this information can be invaluable in determining whether to engage in initial developmental tasks. Due to the brevity of the book, however, its descriptions of the activities do not provide specific direction on the accomplishment of each task. Instead, it admonishes physicians that "selection of a consulting firm to assist the physician group with the feasibility study, development of the HMO and, possibly, management of the HMO is a very important task." The lack of substantive guidance for assessment of consultants' performance is a drawback for those who are not well-versed in such appraisals.

Almost as an afterthought, a section on Medicare and Medicaid HMOs is included as the final chapter. HMOs serving the Medicare and Medicaid populations must meet certain requirements in their eligibility and operations and those complexities are described in a clear and straightforward manner. This chapter is well worth reading simply for the explanation of how the Adjusted Community Rate, or the premium a Medicare HMO would charge its enrollees, is computed.

In summary, physicians will find the book useful in delineating the activities of HMO development and as a checklist in completing those tasks. After reading it, some physicians may decide against undertaking this monumental task, as it is something not to be approached in a casual manner.

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NEUROLOGY IN PRIMARY CARE—Editor: Robert C. Cantu, MD, Chief, Neurosurgical Service; Associate Chairman, Department of Surgery, and Director, Service of Sports Medicine, Emerson Hospital, Concord, Mass; Associate Editors: Russell B. Butler, MD, Assistant Professor of Neurology, Boston University School of Medicine, and Chief of Neurology, Emerson Hospital, Concord, and Michael J. Moore, MD, Associate Professor of Neurology, Boston University School of Medicine. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1985. 424 pages, $55.

The stated purpose of this book is to provide "a practical and current reference covering all of the commonly encountered disorders of the central nervous system." The editors also state, "we have excluded the esoteric and kept this volume to a manageable length." Unfortunately, however, the editors did not follow the above stated purposes: a significant amount of space has been devoted to neurologic illnesses that can only be considered rare and esoteric. For example, in the chapter devoted to "Disorders of Muscle," the metabolic myopathies received as much attention as did the more common forms of childhood and adult muscular dystrophies. The chapter entitled "Inherited Metabolic Diseases" should not even have been included as each of the disorders is very rare and there are a significant number of conceptual errors present. The author of this chapter classifies the neuronal ceroid lipofuscinoses (Bielschowsky-Jansky, Spielmeyer-Vogt and Kuf's Diseases) along with adrenoleukodystrophy as lysosomal storage diseases. While the enzyme deficiency that causes these disorders remains unknown, there is certainly no evidence that lysosomal enzymes are involved. In fact, all evidence to date suggests that adrenoleukodystrophy is a lipid storage disorder resulting from an enzymatic defect in the "peroxisome."

Many of the chapters in this volume are of high quality and contain much useful information for the "primary care physician" but because of the uneven quality and high cost, this reviewer cannot recommend the book. The "primary care physician" in need of a text covering disorders of the nervous system would be better off purchasing one of the many excellent standard textbooks of neurology.

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* * *

THE SNOWBIRD DIET: 12 Days to a Slender Future—and a Lifetime of Gourmet Eating!—Donald Robertson, MD, MSc, and Carol P. Robertson. Warner Books Hardcover and Trade Paperback, Division of Warner Communications Company, 666 Fifth Avenue, New York, NY 10103, 1986. 290 pages, $8.95.

The Snowbird Diet is a 290-page book that presents a plan formulated by experts in weight management and related fields—bariatrics, nutrition, exercise physiology, psychology and haute cuisine as practiced by the Southwest Bariatric Nutrition Center in Scottsdale, Arizona. This is a complete medical weight loss program that integrates fat loss with fitness, preventive medicine and life extension. This reviewer rates it as a safe, scientific and highly motivating plan that offers real hope for permanent weight management. It treats overweight as a potentially serious medical disease and allows the active high powered people who want to travel, entertain, dine out and enjoy a good life the opportunity to do so while keeping trim and fit. It does not present a fad diet nor a magic cure for overweight persons.

The book is divided into four parts. Part one explains the Snowbird Diet as a 12-day program for weight loss as preventive medicine and life extension. Part two explains how the Snowbird Diet really works and presents the experience of many years of Dr Robertson's practice as an internist and gastroenterologist with much experience in weight reduction. Part three describes the essential details for success of the program. Part four presents the keys to a slender lifetime and the details in entering the normal life without gaining weight. There are a good bibliography and references which include information on exercise, psychological awareness, maintenance, general health and nutrition. The index is detailed.

The term "Snowbird" is derived from the frostbitten Northerners who flock to the Sun Belt for warmth and total revitalization. Dr Robertson is a graduate of Princeton University and Cornell University Medical College, and is a nationally recognized authority on nutrition and weight loss. Carol P. Robertson is Executive Director of the Southwestern Bariatric Nutrition Center and a gourmet cook whose cooking has been featured in many magazines and articles concerning food problems and how to solve them.

This highly readable book is based on a 12-day meal-by-meal eating plan including gourmet recipes and shopping lists. There is an emergency diet for those traveling and dining out that may also be followed by dieters not interested in gourmet meals.

MERLE S. SCHERR, MD
Scottsdale, Arizona

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(Continued from Page 174)

PATHOLOGY

May 21-22—**Annual Meeting: Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Fri. 12 hrs. Contact: UCSF.

PEDIATRICS

February 16-18—**Pediatrics Update 1987.** Continuing Medical Education Associates at Hyatt Islandia Hotel, San Diego. Mon-Wed. 18 hrs. Fee: $275. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 5-7—**Advances in Pediatrics II.** American Academy of Pediatrics at Kauai, Hawaii. Thurs-Sat. 16 hrs. Fee: $330. Contact: Neal A. Baker, Div of Continuing Education, AAP, PO Box 927, Elk Grove Village, IL 60007. (800) 433-9016, or in Illinois (800) 421-0589.

March 12-15—**17th Annual Combined Socal Pediatric Postgraduate Meeting.** American Academy of Pediatrics at Desert Princess Hotel, Palm Springs. Thurs-Sun. Contact: AAP, PO Box 2134, Inglewood 90305. (213) 757-1198.

April 2-4—**20th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

April 8—**Pediatrics: Genetics.** LLU. Wed. 4 hrs. Fee: $60. Contact: LLU.

May 4-7—**Pediatrics in the 80's—The 17th Annual Pediatrics Course.** USC at Marina Beach Hotel, Marina del Rey. Mon-Thurs. 18.5 hrs. $395. Contact: USC—in California, (800) 321-1929, National, (800) 421-6729.

PSYCHIATRY

March 28-29—**The Cutting Edge 1987: Difficult Treatment Problems With Borderline and Narcissistic Patients.** UCSD at Hotel Inter-Continental, San Diego. Sat-Sun. 13 hrs. Contact: UCSD.

April 10-11—**Mental Health in the Workplace.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sat. 11.5 hrs. Fee: $200. Contact: UCSF.

RADIOLOGY

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 23-28—**6th Annual West Coast: Doppler Ultrasound.** Institute for Medical Studies at Newport Beach. Mon-Sat. Contact: Lisa Krehbiel, Inst for Med Studies, 30131 Town Ctr Dr, Ste 215, Laguna Niguel 92677. (714) 495-4499.

March 2-4—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Mon-Wed. Fee: $400. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 2-4—**Neuroradiology Update.** UCSD at Hotel Del Coronado, Coronado. Mon-Wed. Fee: $350. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 2-6—**The Annual Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation at Hyatt Lake Tahoe, Incline Village, Nevada. Mon-Fri. 20 hrs. Fee: $385. Contact: John P. McGahan, MD, SRREF, PO Box 19184, Sacramento 95819.

March 3-5—**MRI for Technologists.** UCSD at Hotel Del Coronado, Coronado. Tues-Thurs. 15.5 hrs. Contact: Dawn Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 3-6—**Magnetic Resonance Imaging.** UCSD at Hotel Del Coronado, Coronado. Tues-Fri. 25 hrs. Contact: Mary J. Ryals, Ryals and Assoc, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

March 7-8—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Sun. Contact: UCSF.

March 9-13—**30th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. Contact: UCSF.

March 14-15—**Contemporary Trends in Diagnostic Nuclear Medicine.** UCSF at Hyatt Regency Hotel, San Francisco. Sat-Sun. Contact: UCSF.

March 16-20—**Diagnostic Imaging—1987.** UCSF at Waiohai Hotel, Kauai, Hawaii. Mon-Fri. Contact: UCSF.

April 9-11—**Thoracic Imaging—1987.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

April 10-12—**OB/GYN and Abdominal Sonography: Update 1987.** UCSF at Hyatt Regency on Union Square, San Francisco. Fri-Sun. Contact: UCSF.

April 13-17—**Vascular Imaging.** University of Washington at Royal Lahaina Resort, Maui, Hawaii. Mon-Fri. Contact: Univ of Washington, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 19-25—**7th Annual San Diego Residents' Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Sat. Contact: UCSD.

May 1-3—**12 Annual Spring Diagnostic Ultrasound.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 19.5 hrs. Fee: $325. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

May 5-9—**7th Annual Diagnostic Ultrasound Post Conference Seminar.** Los Angeles Radiological Society at Sheraton Princeville Hotel, Kauai, Hawaii. Tues-Sat. 19 hrs. Fee: $395. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 14-16—**1987 Radiology US Open Golf Meeting.** UCSF at Hyatt Regency, San Francisco. Sun-Tues. Contact: UCSF.

SPORTS MEDICINE

March 16-20—**Annual University of Hawaii: Sports Medicine.** Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Mon-Fri. 18 hrs. Fee: $300. Contact: Ms Joy Lewis, Box CEW-CCECS, 2530 Dole St, Honolulu, HI 96822. (808) 948-8244.

SURGERY

February 17-19—**Maxillofacial Trauma.** USC. Tues-Thurs. 16 hrs. Fee: $500. Contact: USC.

February 22-28—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 5-8—**37th Annual Surgical Forum.** Society of Graduate Surgeons of Los Angeles County at Ambassador Hotel, Los Angeles. Thurs-Sun. 25 hrs. Contact: Soc of Grad Surgeons, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

March 6-8—**Cruciate Ligament Surgery: Principles and Practice.** Scripps Clinic and Research Foundation at Marriott Hotel, La Jolla. Fri-Sun. 23 hrs. Contact: Bonny A. Mower, Dept of Academic Affairs, Box 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 8-14—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

March 18-20—**Preoperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. Fee: $325. Contact: UCSF.

March 30-April 10—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Mon-Fri. 100 hrs. Fee: $1,750. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

April 11-18—**Surgery.** University of Washington at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: University of Washington School of Medicine, Div of CME, Sc-50, Seattle, WA 98195. (206) 543-1050.

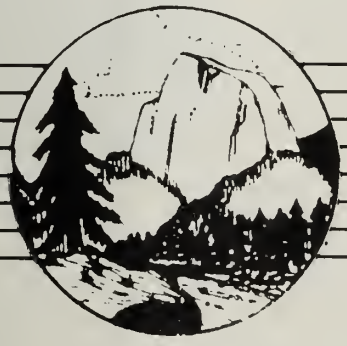
April 30-May 2—**American Back Society Spring Symposium.** Anaheim Hilton Hotel. Thurs-Sat. Contact: Aubrey A. Swartz, American Back Soc, 2647 E. 14th St, Ste 401, Oakland 94601. (415) 536-9929.

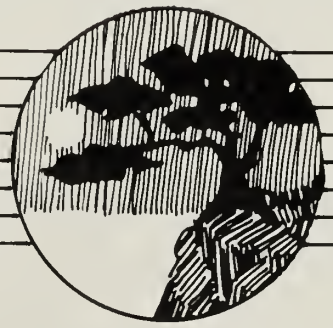
April 30-May 2—**Postgraduate Course in General Surgery.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

May 11-15—**The San Francisco Orthopaedic Review Course.** UCSF at San Francisco. Mon-Fri. 40 hrs. Contact: UCSF.

(Continued on Page 254)

Regional Postgraduate Institutes





San Joaquin Valley Counties

Curry Village, Yosemite
April 23-25, 1987

- Advances in Immunology
- Chemical Dependency, Drug Testing and Intervention
- Ability Versus Disability
- Prostatic Inflammatory Disease
- Treatment for Renal Stone Disease
- Update on AIDS
- Medical Economics
- Male Infertility
- New Prospectives in Toxicology
- Medications and Pregnancy
- Different Approaches to Problem of Depression

West Coast Counties

Monterey Sheraton
October 22-24, 1987

- Update for Primary Care physicians

The content of these programs has been determined by the educational needs of primary care physicians as perceived and translated by the members of the Planning Committee.

These programs are accredited for Category One credit for Physicians and Registered Nurses
Hotel space is limited—early reservations are suggested.

Complete program and hotel information will be sent by return mail.
Use the tear-off sheet below or call CMA (415) 863-5522, extension 416.

I plan to attend the following Postgraduate Institute(s):

☐ **San Joaquin Valley Counties**
Curry Village, Yosemite
April 23-25, 1987

☐ **West Coast Counties**
Monterey Sheraton
October 22-24, 1987

FEE: $150 for each institute
($200 for Non-CMA members)
Please make check payable to California Medical Association

Name _____

Specialty _____

Address _____

City _____ County _____ Zip _____

Number of years out of medical school _____

Mail to: California Medical Association, P.O. Box 7690, San Francisco, CA 94120-7690
Attn: Janice Rigney. A program and hotel reservation form will be sent to you.

(Continued from Page 252)

May 13—**Otolaryngology: ENT Infections.** LLU at LLU. Wed. 4 hrs. Fee: $60. Contact: LLU.

May 14-16—**Symposium on the Temporomandibular Joint.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

June 4-5—**16th Annual Neurosurgical Postgraduate Course.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

June 14-20—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. 62 hrs. Fee: $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

February 16-18—**7th Annual Betty Ford Center Conference on Alcoholism/Chemical Dependency: Chemical Dependency/Mental Illness—Issues in Diagnosis and Treatment.** Eisenhower Medical Center, Rancho Mirage. Mon-Wed. 17 hrs. Contact: Jacqueline Lycett, Annenberg Center, 39000 Bob Hope Dr, Rancho Mirage 92270-3298. In California, (800) 621-7322, nationally, (800) 321-3690.

February 18-19—**Sexually Transmitted Disease (STD) Update for Clinicians.** Long Beach Health Dept and UCI at Long Beach. Wed-Thurs. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

February 21-28—**Radiology for Emergency and Primary Care Physicians.** Scripps Memorial Hospital, Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. Fee: $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 23-27—**Basic Science for Clinicians.** STAN. Mon-Fri. 25 hrs. Fee: $450. Contact: STAN.

February 25—**Human Immunodeficiency Virus (HIV): An Introductory Course for Primary Care Physicians.** County of Riverside—Dept of Health at Sheraton Hotel, Riverside. Wed. Contact: Anne Gregory, Dept of Health, PO Box 1370, Riverside 92502. (714) 787-2167.

March 4-6—**37th Annual Course for Physicians in Family Practice: Therapeutic Advances in Family Practice.** Mt Zion Hospital and Medical Center, San Francisco. Wed-Fri. Contact: Robin B. Jackson, Medical Staff and Education Office, Mt Zion Hospital, PO Box 7921, San Francisco 94120. (415) 885-7261.

March 6-12—**55th Annual Postgraduate Convention.** LLU Alumni Association at LLU. Fri-Thurs. 35 hrs. Contact: Carolyn Wieder, LLU, (714) 824-4633.

March 7-8 and 21-22—**Annual Workshop.** San Francisco Academy of Hypnosis at Letterman Army Medical Center, San Francisco. Sat-Sun. 28 hrs. Fee: $300. Contact: Jan Brooks, 615-27th St, San Franicsco 94131. (415) 826-0533.

March 8—**Pharmacotherapeutic Interventions in the Treatment of Chemical Dependence—Drug Solutions for Drug Problems.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Anaheim. Sun. 5 hrs. Contact: Sandy Swift, Cal Soc for the Treatment of Alcoholism and Other Drug Dependencies, 3803 Broadway, #2, Oakland 94611. (415) 428-9091.

March 9-13—**Hawaii '87: Critical Issues in Primary Care.** Hawaii Medical Association at Waiohai Hotel, Poipu Beach. Mon-Fri. 20 hrs. Contact: Valerie Murray, Pacfic Institute of Continuing Medical Education, PO Box 1059, Koloa, Kauai, HI 96756. 1 (808) 742-7471.

March 11—**Geriatrics.** Enloe Hospital, Chico. Wed. Contact: Linda Morgado, Enloe Hospital, W 5th Ave and The Esplanade, Chico 95926. (916) 891-7300.

March 13-15—**Office Emergencies in Primary Care.** Sharp Memorial Hospital at Hotel Del Coronado, Coronado. Fri-Sun. 18 hrs. Fee: $325. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

March 16-20—**Epidemics, Pandemics, and Mass Hysteria: From Antiquity to AIDS.** Kauai Foundation for Continuing Education at Poipu Beach, Kauai, Hawaii. Mon-Fri. 19 hrs. Contact: David J. Elpern, MD, Kauai Foundation for Continuing Education, PO Box 3650, Lihue, HI 96766. (808) 245-1507.

March 16-27—**Sexually Transmitted Disease (STD) Clinician Trng Course—Comprehensive.** Long Beach Health Dept and UCI at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, Long Beach 90806. (213) 427-7421.

March 19-27—**Specialty Series in Primary Care: Cardiology, Infectious Diseases and Endocrinology.** UCSD at Palm Springs Spa Hotel. Thurs-Fri. Contact: UCSD.

March 26-28—**CPR Update/ACLS Recertification.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Sat. 21.5 hrs. Fee: $350. Contact: UCSF.

March 28—**Management of the Menopause: Osteoporosis and Estrogen Replacement Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Fee: $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 30-April 2—**Perspectives in Family Practice.** UCLA at King Kamehameah Hotel, Kona, Hawaii. Mon-Thurs. 20 hrs. $400. Contact: UCLA.

April 6-10—**Drug Therapy.** University of Washington at Kona Surf Resort, Hawaii. Mon-Fri. Contact: Univ of Washington, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 13-17—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept and UCI at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

April 20-23—**Selected Topics in Dermatology and Pulmonary Intensive Care.** LLU at LLU. Mon-Thurs. 16 hrs. Fee: $400. Contact: LLU.

April 25-26—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, La Jolla. Sat-Sun. 13.5 hrs. Fee: $275-400. Contact: UCSD.

May 11-12—**6th Annual Physical Abuse: The Traumatized Child and Family.** UCD at Sacramento Inn. Mon-Tues. 11 hrs. $100. Contact: UCD.

May 11-13—**Arthritis Update '87.** Sharp Memorial Hospital, San Diego and UCSD at Hyatt Islandia Hotel, San Diego. Mon-Wed. Contact: Mary Belich, Sharp Memorial Hospital, 7901 Frost St, San Diego 92123-2788. (619) 541-3400.

June 8-13—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Mon-Sat. Contact: UCI.

June 15-19—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept and UCI at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

June 28-29—**9th Annual Poison Control Center: Management of Drug Overdose and Poisoning.** UCSF at San Francisco. Sun-Mon. 14 hrs. $235. Contact: UCSF.

July 6-9—**Family Practice Board Review.** UCSF at UCSF. Mon-Thurs. 25 hrs. Contact: UCSF.

IDAHO

February 21-28—**Maternal-Fetal Medicine.** Sun Valley. One week. Sponsor: University of Washington School of Medicine. Contact: U/W School of Medicine, Division of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 27-March 1—**Personal Fitness for You and Your Patient: Speakers From the Cleveland Clinic.** Shore Lodge, McCall. Fri-Sun. Sponsor: Ada County Medical Society. 11 hrs. Fee: $125. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

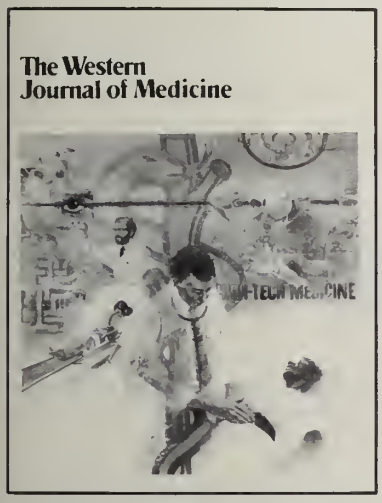
(Continued on Page 256)

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

High-Tech Medicine



Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

SPECIAL ISSUES

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A WORD TO THE WHYS

WHY AMA? The AMA has taken an important initiative in combating prescription drug abuse. An informal steering committee organized by the AMA has developed a data analysis system that would help states detect sources of prescription drug diversion. Cracking down on prescription drug abuse: it's one more good reason why you should be part of the AMA.

WHY AMA? The AMA has actively sought to attract women as members and leaders in organized medicine. Ongoing AMA projects and concentrated efforts by county, state, and specialty societies have significantly increased the leadership role and membership of women in organized medicine. Strengthening the voice of women in medicine through encouraging active participation: it's one more good reason why you should be a part of the AMA.

To Join, Contact your county or state medical society or write: Division of Membership, AMA, 535 North Dearborn Street, Chicago, Illinois 60610 or call collect, (312) 751-6196.

AMA AMERICAN MEDICAL ASSOCIATION

(Continued from Page 254)

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 19-21—**Sports Medicine.** Tammaron. Thurs-Sat. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

February 20-22—**15th Annual Taos Lung Disease Symposium.** Taos. Fri-Sun. Contact: NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

February 27-28—**Advances in Internal Medicine VII.** Albuquerque. Fri-Sat. VAMC Conference Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 5-7—**20th Annual Ob/Gyn Postgraduate Seminar.** Albuquerque. Thurs-Sat. Hilton. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 11-14—**New Mexico Metabolism Symposium.** Taos. Wed-Sat. Quail Ridge Lodge. Contact: Lovelace Medical Foundation, Office of Medical Education, 2425 Ridgecrest Dr SE, Albuquerque 87108. (505) 262-7353.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Sat. Contact: NM Pediatric Society, (505) 758-8651.

March 14—**Perfecting Your Cardiac Physical Diagnosis Techniques: Lessons From a Master—A Symposium by W. Proctor Harvey, MD.** Albuquerque. Sat. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

March 19-20—**Cultural Issues in Family Therapy.** Albuquerque. Thurs-Fri. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

April 9-11—**9th Annual Pediatric Cardiopulmonary Update.** Albuquerque. Thurs-Sat. AMFAC Hotel. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

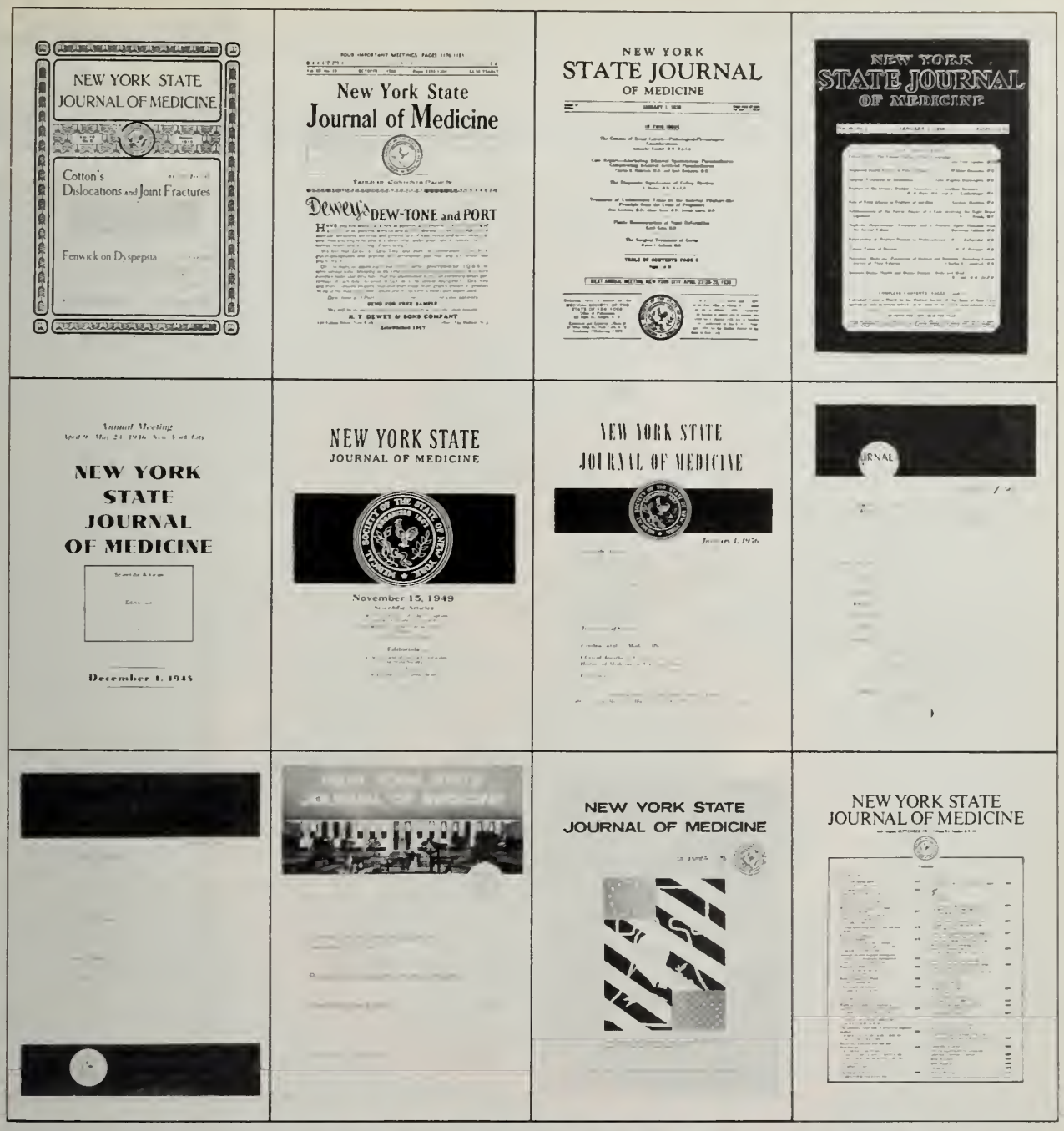
April 24-25—**Practical Orthopaedics in the Primary Care Setting.** Albuquerque. Fri-Sat. Veterans Administration Medical Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

May 6-8—**New Mexico Medical Society—Annual Meeting.** Albuquerque. Wed-Fri. Clarion Four Seasons. Contact: NMMS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

May 15-16—**Biological and Ethical Dimensions of Human Transplantation.** Albuquerque. Fri-Sat. Contact: Office of Medical Education, Presbyterian Hospital, PO Box 26666, Albuquerque 87125. (505) 841-1225.

(Continued on Page 258)

Cover to cover . . . . always good reading.



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(Continued from Page 256)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 14-21—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). One week. Park City Resort. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 19-21—**Mid-Winter Trauma Seminar for Military and Civilians** (Sponsor: UUMC). Thurs-Sat. Westin Hotel Utah, Salt Lake City. 15 hrs. Contact: Clayton Petty, MD, (801) 581-6393.

February 20-24—**Postgraduate Course in Anesthesiology** (Sponsor: UUMC). Fri-Tues. Salt Lake City. 16 hrs. Contact: Theodore Stanley, MD, (801) 581-6393.

February 21-25—**Annual Ob-Gyn Update** (Sponsor: UUMC). Sat-Wed. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 22-27—**Park City Dermatology Seminar** (Sponsor: UUMC). Sun-Fri. Park City. 18 hrs. Contact: Gerald Kruegar, MD, (801) 581-7837.

February 23-27—**Surgical Pathology Workshops** (Sponsor: UUMC). Mon-Fri. The Yarrow, Park City. 20 hrs. Contact: Tom Colby, MD, (801) 581-7480.

February 25-28—**Gynecologic Oncology** (Sponsor: UUMC). Wed-Sat. Park City. 15 hrs. Contact: James Scott, MD, (801) 581-5501.

February 26-28—**Arthroscopic Surgery** (Sponsor: UUMC). Thurs-Sat. Westin Hotel Utah, Salt Lake City. 21 hrs. Contact: Robert Metcalf, MD, (801) 581-7601.

March 2-6—**Advances in Internal Medicine.** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-7801.

March 8-13—**Diagnostic Imaging and Interventional Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird Resort. 20 hrs. Contact: Judy Gallegos, (801) 581-8188.

March 9-13—**Medical and Surgical Advances in GI** (Sponsor: UUMC). Mon-Fri. Snowbird Resort. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 9-14—**Advanced Rheumatology 1987** (Sponsor: UUMC). Mon-Sat. Snowbird Resort. 20 hrs. Contact: John Ward, MD, (801) 581-8664.

March 11-13—**9th Annual Common Problems in Pediatrics** (Sponsor: UUMC). Wed-Fri. Salt Lake Hilton. 14 hrs. Contact: Katharine Blosch, (801) 466-3500.

March 16-20—**Nutrition in Contemporary Medicine** (Sponsor: UUMC). Mon-Fri. Park City. 30 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 20—**Diabetes and Nutrition Update** (Sponsor: UUMC). Fri. Univ of Utah, Salt Lake City. 8 hrs. Contact: (801) 581-5809.

March 26-28—**Neurology for the Practitioner** (Sponsor: UUMC). Thurs-Sat. Salt Lake City. 15 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

April 6-8—**Genetic Testing and New Biomedical Technologies in the Prevention of Occupational and Environmental Disease** (Sponsor: UUMC). Mon-Wed. Park City. 18 hrs. Contact: Connie Crandall, (801) 581-8719.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 19-20—**Sexual Assault: Advances in Medical-Legal Issues.** Seattle. Thurs-Fri. Contact: Sexual Assault Center, Harborview Medical Center, 325 Ninth Ave, Seattle 98104. (206) 223-3047.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 273)

24-hour security for the hypertensive heart

First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial O_2 demand

Preserves K^+ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

Once-a-day in hypertension...

Lopressor®
metoprolol tartrate

Changing the Course of Cardiovascular Care

Geigy

First-step protection for the hypertensive heart

Lopressor®
metoprolol tartrate USP

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0 24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously Both digitalis and Lopressor slow AV conduction

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken Patients should be warned against interruption or discontinuation of therapy without the physician's advice Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e g , tachycardia) of hyperthyroidism Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients, this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0 26 sec), second-, or third-degree heart block Acute myocardial infarction also produces heart block

If heart block occurs, Lopressor should be discontinued and atropine (0 25-0 5 mg) should be administered intravenously If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may oe required Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is *unknown* to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals If a dose should be missed, the patient should take only the next scheduled dose (without doubling it) Patients should not discontinue Lopressor without consulting the physician

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined, (2) to contact the physician if any difficulty in breathing occurs, (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase
Drug Interactions
Catecholamine-depleting drugs (e g , reserpine) may have an additive effect when given with beta-blocking agents Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia Neither finding represents symptoms of a known disease entity in man In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55 5 times the maximum daily human dose of 450 mg
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55 5 times the maximum daily human dose of 450 mg Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal These studies have revealed no evidence of impaired fertility or teratogenicity There are no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients Depression has been reported in about 5 of 100 patients Mental confusion and short-term memory loss have been reported Headache, nightmares, and insomnia have also been reported

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients Cold extremities, arterial insufficiency, usually of the Raynaud type; palpitations, congestive heart failure, peripheral edema, and hypotension have been reported in about 1 of 100 patients (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients Worsening of psoriasis has also been reported

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes Discontinuation of the drug should be considered if any such reaction is not otherwise explicable

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27 4%	23 2%
Bradycardia (heart rate < 40 beats/min)	15 9%	6.7%
Second- or third-degree heart block	4.7%	4 7%
First-degree heart block (P-R ≥ 0 26 sec)	5 3%	1 9%
Heart failure	27.5%	29 6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death

Oral LD_{50}'s (mg/kg): mice, 1158-2460, rats, 3090-4670
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure
Treatment
There is no specific antidote

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously

Hypotension: A vasopressor should be administered, e g , levarterenol or dopamine

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered

Cardiac Failure: A digitalis glycoside and diuretic should be administered In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

Geigy GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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TUCSON ARIZONA: Urgent Care, Family Practice, Internal Medicine, Pediatrics, OB/GYN. CIGNA Healthplan has career opportunities in Tucson, Arizona. Join a distinguished staff of experienced physicians; practice medicine without the administrative demands of private practice. Professional liability coverage, pension and retirement benefits, scheduled working hours, paid vacations, and CME benefits are provided along with a competitive salary. Please submit CV to: Director of Physician Recruitment, CIGNA Healthplan of Arizona, Inc., 4907 E. Broadway, Ste. 100, Tucson, AZ 85711; (602) 571-6517. Equal Opportunity Employer M/F/H/V.

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SAN FRANCISCO BAY AREA. Family Practitioner, Board-eligible or Board-certified, to join large multispecialty, prepaid group practice. Excellent fringe benefits. Superb environment. Contact James Conroy, MD, The Permanente Medical Group, Inc., 260 International Circle, San Jose, CA 95119. Telephone (408) 972-3276. Or call collect to (408) 972-3000.

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GENERAL SURGEON—Immediate position available to join a busy, established solo practice in northwestern Arizona. Current physician nearing retirement. 82 bed hospital one block away. New office in desert community in rapidly growing area of 18,000 on the Colorado River. Referral area of 68,000. Please send CV to Number 4, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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NORTHERN CALIFORNIA. Family Practitioner wanted to join two FP's in private practice which includes OB. No initial overhead, income guarantee. Modern office across from 65 bed community hospital with staffed ER. Contact Michael Jennings, MD, 2540 Sr. Mary Columba Dr., Red Bluff, CA 96080; (916) 527-3424.

CALIFORNIA, SAN FRANCISCO BAY AREA: Full-time career Emergency Physician wanted for high volume Emergency Department. Emergency Medicine Board certified or Board-ready mandatory to participate in a group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation; one week CME, paid malpractice, health and life insurance; corporate shareholdership in three years. Send CV or contact David Gallagher, MD, 27400 Hesperian Blvd., Hayward, CA 94545.

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GENERAL INTERNIST. Multispecialty group of 30 physicians has immediate positions available for Board certified or eligible General Internists. The growth oriented Group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Estimated starting date of March 1, 1987. City is a great place to raise a family in a clean environment. Send résumé to: Recruitment, 2705 Loma Vista Rd., Ventura, CA 93003.

ORTHOPEDIST. Multispecialty group of 30 physicians has immediate position available for Board certified or eligible Orthopedist. The growth oriented Group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. City is a great place to raise a family in a clean environment. Send résumé to: Recruitment, 2705 Loma Vista Rd., Ventura, CA 93003. Estimated starting date of March 1, 1987.

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(Continued on Page 270)

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Here's the Scoop...

on the California Medical Association's
116th Annual Session & Western Scientific Assembly
March 6-11, 1987 ◆ Disneyland Hotel, Anaheim

The Inside Scoop on the

Lloyd H. Smith, Jr., MD

Lloyd H. Smith, Jr., MD, San Francisco, has been selected by the Committee on Scientific Assemblies to receive CMA's 1987 Golden Apple Award. This award spotlights outstanding physician speakers who have made a lifelong commitment to teaching and become distinguished by their charismatic, scientific and educational talents.

FRIDAY, MARCH 6

- ❑ Advanced Cardiac Life Support Workshop: Recertification Course*
- ❑ Internal Medicine Update
- ❑ The Surgically Treatable Dementias: Alternatives to the Nursing Home
- ❑ Doctor—When Can I Work? Impaired Workers and Limited Work Assignments
- ❑ Management of Neck and Upper Extremity Pain
- ❑ Violence and Its Impact on the Family
- ❑ Special Topics on Benzodiazepines
- ❑ Current Issues in Developmental Disabilities
- ❑ Treating Chronic Benign Pain in High-Risk Patients
- ❑ Programmed Instruction on Autotutor Machines

*There is also a two-day ACLS *Certification* Course Thursday and Friday, March 5-6.

- ❑ Golden Apple Award: Lloyd H. Smith, Jr., M.D.

SATURDAY, MARCH 7

- ❑ Recognition and Treatment of Melanoma and Other Important Skin Lesions of the Head and Neck
- ❑ Basic Cardiac Life Support
- ❑ Environmental Emergencies
- ❑ Trauma in the '80s: Blood and Red Ink
- ❑ Clinical Update on the Spine
- ❑ Pain Mechanisms and Management
- ❑ Update on Radiation Problems Including Chernobyl
- ❑ Hormonal Therapy in Women
- ❑ Endoscopic Nasal Sinus Surgery
- ❑ Breast Cancer: A to Z
- ❑ AIDS Update for the Practicing Physician
- ❑ Medical Jurisprudence for Residents and Former Residents
- ❑ Psychic Band-Aids II: Doctoring for the Mental Abrasions of Medical School
- ❑ Matchmaking: A Workshop on Residency Selection and Career Planning
- ❑ Cocaine: Treating the New Addiction
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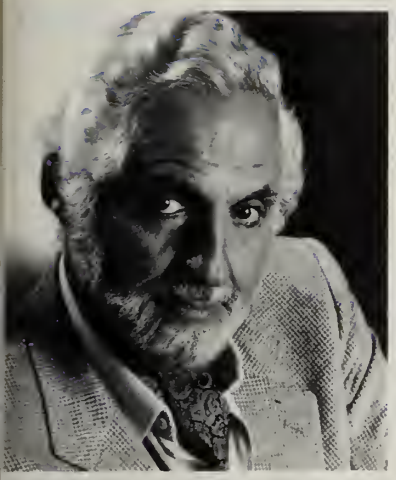
Western Scientific Assembly



PROFESSOR CARL DJERASSI
Keynote Speaker

DENNIS O'LEARY, MD
JCAH President

SUNDAY, MARCH 8

- ❑ Allergy, Immunology and the Skin: What's New and Clinically Important
- ❑ Rational, Effective and Attainable Methods of Postoperative Pain Control
- ❑ Colorectal Cancer Screening: Flexible Sigmoidoscopy/Short Colonoscopy and Endoscopic Biopsy
- ❑ Eye Care for the Primary Care Physician
- ❑ Symposium on Osteoporosis—Diagnosis and Treatment
- ❑ Advances in Pediatric Nutrition
- ❑ Suture Course
- ❑ Trauma Update
- ❑ What the Primary Care Physician Should Know About Urology in 1987
- ❑ A Critical Look at the Washington Scene
- ❑ Marketing Roundtable
- ❑ Young Physicians in Organized Medicine: Leadership Roles for a New Generation
- ❑ Programmed Instruction on Autotutor Machines
- ❑ Keynote Speaker: Professor Carl Djerassi
  Birth Control in the Year 2001: Scientific Possibilities and Political Realities

MONDAY, MARCH 9

- ❑ Controversies in Chest Medicine—1987
- ❑ Topics in Family Medicine
- ❑ Primer on Physician Contracting
- ❑ The ABCs of IPAs: Structures, Relationships and Legal Issues
- ❑ Programmed Instruction on Autotutor Machines

EXHIBITS

Visit the Exhibit Hall Friday through Sunday and see pharmaceuticals, educational displays, computer systems, office systems, medical testing systems, health services, insurance, investment opportunities, health helps and home helps. Prizes!

The Inside Scoop on the Western Scientific Assembly...

CONCURRENT EVENTS

HOUSE OF DELEGATES

The CMA House of Delegates meets each day, Saturday through Wednesday. Sit in on reference committee hearings and House sessions to see firsthand how CMA policies are shaped. Highlights of this year's House will be the farewell address of outgoing CMA President Dr. Gladden V. Elliott, a San Diego radiologist, and the inaugural address of CMA's President-Elect, Dr. Frederick S. Armstrong, a San Jose internist.

HOSPITAL MEDICAL STAFF SECTION ANNUAL ASSEMBLY

The CMA-HMSS Annual Assembly will be Friday, March 6. Included will be an educational conference, "Medical Staff Issues: 1987," keynoted by Dennis O'Leary, MD, JCAH President.

SPECIAL EVENTS

A variety of special tours and programs will be offered, including:

- ❑ J. Paul Getty Museum
- ❑ Gump's Presents Gems in General
- ❑ L.A.'s Garment District
- ❑ Newport Bay Harbor Cruise and Dinner
- ❑ The Silver Screen—The Inside Look
- ❑ Early California Tour
- ❑ Aerobics Classes
- ❑ Family Fun Day at Disneyland

GENERAL INFORMATION

LOCATION

The CMA 1987 Annual Session and Western Scientific Assembly will be headquartered in the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, California, 92802. Room reservations will be accepted on a "space available" basis. Call (714) 778-6600 for reservation information.

FEES

There is no general registration fee for CMA members and their nonphysician family members, or for residents, interns, medical students, nurses and allied health professionals. There is a $150 general registration fee for physicians who are not members of the CMA.

REGISTRATION

Advance registration closes February 13, 1987. Attendees may register on-site in the Center Lounge, the foyer outside the Grand Ballroom of the Disneyland Hotel. Registration will be open:

Thursday, March 5	–	1:00 pm to 5:00 pm
Friday, March 6	–	7:30 am to 5:00 pm
Saturday, March 7	–	7:00 am to 5:00 pm
Sunday, March 8	–	7:30 am to 4:00 pm
Monday, March 9	–	7:30 am to 5:00 pm

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General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM Except in rare occurrences, these experiences have not caused discontinuation of therapy.

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients

One patient in the clinical trials developed anaphylaxis

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

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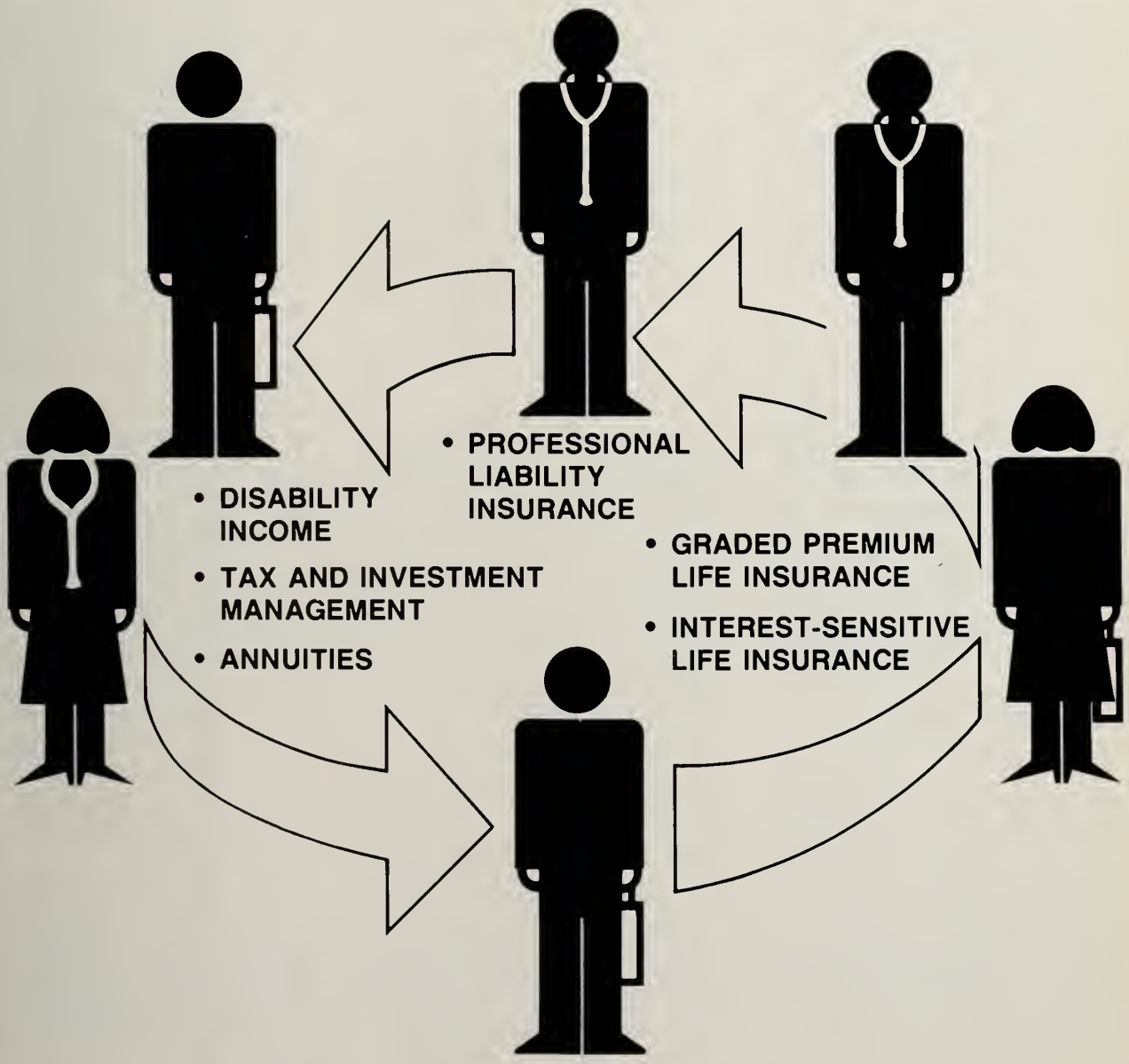

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(Continued from Page 261)

PHYSICIANS WANTED

EDMONDS, WASHINGTON: Scenic waterfront community 20 minutes north of Seattle. Physician owned clinic combined OB/GYN and Family Practice seeks additional OB/GYN for full- or part-time. We presently have 4 Family Practitioners and 2 OB/GYNs. Send CV to Philip DuBois, MD, 7935 216th St. S.W., Suite E, Edmonds, WA 98020; (206) 775-0681.

FAMILY PRACTICE PHYSICIAN—provide primary care in clinics in rural New Mexico; some hospital; ER service; Obstetrics a must. Locations in Cuba, New Mexico, near the Jemez Mountains with skiing and mountain sports nearby. Board certified or Board eligible family practice desired. Excellent benefits. Please call Pat Sanchez, Personnel Director, Presbyterian Medical Services, PO Box 2267, Santa Fe, NM 87504; (505) 982-5565.

GENETIC RESEARCHER AND COORDINATOR. Conduct cytogenetic and genetic research and service. Write articles for US Journals after completion of research. MS or equivalent in cytogenetics, 2 years experience, salary $30,000 per year, job site and interviews Alhambra, California. Send this ad and résumé to Job #DC-10994, PO Box 9560, Sacramento, CA 95823-0560 no later than March 10, 1987.

MEDICAL DIRECTOR—519 bed UCLA affiliated multi-level long term care geriatric facility in the San Fernando Valley is seeking a full-time physician with special education and training in Geriatric Medicine. Candidates should have sufficient academic geriatric credentials acceptable to the academic teaching community. Major duties include but are not limited to supervision and coordination of care provided by the primary and consulting physicians, coordination of medical care with counterpart at sister facility, a direct patient care case load and supervision of Geriatric Fellows when assigned to the facility. Individual must have excellent interpersonal skills to interact with a diverse group of professional staff members. Salary is negotiable based on experience. Excellent fringe benefits. Contact Martin Gittleman, Administrator, Victory Village of the Jewish Homes for the Aging, 18855 Victory Blvd., Reseda, CA 91335.

GENERAL PSYCHIATRIST
Everett, Washington

Excellent opportunity for a psychiatrist in a growing community near Seattle, Washington. Work in a progressive Mental Health Service with a 27 bed inpatient unit with various treatment programs designed to meet a variety of community needs. Potential for affiliation with pre-existing Psychiatric group offering a wide variety of outpatient services. Numerous opportunities for consultation in the immediate community. Must be able to work effectively within an interdisciplinary team model of patient care delivery. Prefer several years post residency training and a community psychiatry orientation. Please contact Dave McConnell, MD, Medical Director, Mental Health Service, The General Hospital of Everett, PO Box 1147, Everett, Washington, 98206; (206) 258-6360.

BOARD ELIGIBLE/BOARD CERTIFIED FAMILY PRACTITIONER needed for Urban Community Health Center. Must do OB. Full privileges in Level II Hospital. Good mix of patients. Excellent support services. Send CV and copy of license to Dr Karen Skarda, Claretian Medical Center, 2945 E. 91st St., Chicago, IL 60617.

MEDICAL DIRECTOR POSITION. Providence Medical Center in Seattle is soliciting applications for the position of Medical Director. Applicants interested in further information concerning job description and position qualifications should contact either Peter Bigelow, Administrator at Providence Medical Center, or Gerold F. Garrett, MD, Chairman of the Medical Director Search Committee. Inquiries to either of these individuals should be directed to Providence Medical Center, 500-17th Ave., Seattle, WA 98124.

PHYSICIANS WANTED

SAN DIEGO

Busy, multispecialty group in San Diego is expanding and will be adding Specialists and Family Physicians to its staff. Outstanding practice opportunities in an ideal geographic setting. For immediate consideration, please send CV to: Miriam Stephens, Director of Professional Recruitment, SMITH HANNA Medical Group, 5703 Oberlin Dr., Ste. 302-49, San Diego, CA 92121.

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Several multispecialty groups and hospitals have asked us to recruit for over 200 positions of various specialties.

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PROJECT USA

Project USA is an AMA program to recruit fully licensed physicians for short-term, general medicine assignments at Indian Health Service (IHS) and National Service Corps (NHSC) hospitals and clinics.

The majority of vacancies are for two weeks, with some extending to four weeks. Participating physicians receive $750 a week at IHS facilities, and $500 a week at NHSC clinics. The doctors are reimbursed for round trip transportation expenses, and living accommodations are provided. Interested physicians are asked to contact John Naughton, Project USA Director, AMA, 535 N. Dearborn, Chicago, Illinois 60610 or call (312) 645-4702.

NEPHROLOGIST wanted for busy Internal Medicine and Nephrology practice near Seattle. Position available immediately. Reply Number 6, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ACUTE CARE EMERGENCY PHYSICIAN/INTERNIST needed to augment existing walk-in service in an 85-member multispecialty clinic. Expanded physical facility under construction. Low level trauma. Emphasis on internal medicine, cardiopulmonary, orthopedics and pediatrics. Short associate status leading to full membership. Incentive oriented compensation. Within 1½ to 2½ hours of Carmel, San Francisco, Yosemite and Lake Tahoe. Reply with CV and references to C. R. Maino, MD, Medical Director, Gould Medical Foundation, 600 Coffee Road, Modesto, CA 95355.

FAMILY PHYSICIAN for growing innovative family health center in San Francisco Bay Peninsula. Practice OB and newborn to geriatrics. No major surgery. Health education emphasis. Multidisciplinary team. POMR. Abundant education and teaching opportunity. Ideal living. ABFP certified residency preferred. Women applicants encouraged. EOE. Salary negotiable. Contact: J Hopkins, MD, 704 Webster, Palo Alto, CA 94301; (415) 324-1940.

FAMILY PRACTITIONER/MEDICAL DIRECTOR—Board certified/eligible for Urban Indian comprehensive care clinic beginning July 1, 1987. Vitae and letter by March 31 to Steven Kelly-Reif, MD, Sacramento Urban Indian Health Project, 801 Broadway, Suite B, Sacramento, CA 95818.

PHYSICIANS WANTED

INTERNAL MEDICINE—Seeking Internist to join established, growing two-person group in Pasadena. Teaching hospital affiliation, liberal vacation policy. Immediate opening—guaranteed initial salary with opportunity for profit-sharing. Reply to Number 5, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OCEANS SHORES, WASHINGTON: Half- to full-time physician position. Ownership potential. Excellent diversity and professional opportunity. Reply Ocean Shores Clinic, PO Box 1178, Ocean Shores, WA 98569; (206) 289-3378.

FAMILY PRACTICE PHYSICIAN: Challenging position available for board-certified FP physician to work in consortium of three rural community health centers in Southern Arizona. Centers located 45 minutes driving time from Tucson, Arizona. Financial arrangements negotiable. Available July 1987. Reply: Peggy A. Broussard, AHPR, 3131 E. Second St., Tucson, AZ 85716; (602) 626-7946.

EMERGENCY MEDICINE PRACTICE seeks physician in high volume practice. Must be Board certified in Emergency Medicine or currently taking Boards; must be Board certified in industrial medicine or experience in medical disability and rehabilitation. MD degree with major in Medicine required. Forty hours per week, 8-12 am and 1-5 pm, $40 per hour. Qualified applicants send résumé or application letter to: AZ DES Job Service, Attention: 732-A, Re: 0802253, PO Box 6123, Phoenix, AZ 85005. Job location: Mesa. Employer paid ad; proof of authorization to work in US required; list in résumé or application letter.

PEDIATRICIAN—SEATTLE AREA. Full-time, also possible part-time. Join group of five. Send CV and availability date. Children's Clinic, 21616-76th Ave., W, #108, Edmonds, WA 98020.

PARTNER SOUGHT. North Puget Sound GP/FP BC/BE. Great opportunity. New building. Expanding military facility with large dependant and retired population. Super recreational and leisure area. Call (206) 675-9739 or write Hugh T. Beatty MD, 3135 Robin Ln., Oak Harbor, WA 98277.

OCCUPATIONAL/INDUSTRIAL MEDICINE. Rare opportunity for physician—BC/BE Emergency Medicine or Occupational Medicine (with ER experience)—to join LARGE, well established Industrial Medicine practice. Seeking dynamic, motivated individual possessing strong clinical skills. Ideal candidate would also enjoy interfacing with employers, insurance companies and other members of the safety and health care team. Excellent income potential and benefits. Please reply to Kathleen Daniel, Occupational Health Services Coordinator, 2100 "F" St., Suite 240, Bakersfield, CA 93301; (805) 324-8811.

INTERNAL MEDICINE—San Francisco suburb. BC/BE associate needed for busy solo practice adjacent to Mount Diablo Hospital. Send CV to: Number 9, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

DIRECTOR OF THE STUDENT HEALTH CENTER. Sonoma State University invites applications for the Director of the Student Health Center. The University is located 48 miles north of San Francisco and is part of the California State University system. The Director administers a comprehensive outpatient medical clinic, and shares with other physicians the care of approximately 6,000 students. A valid California Medical license is required at the time of employment, along with five years experience in the practice of medicine, exclusive of internship, at least one year must be administratively related. For complete job announcement, required qualifications and application procedures, please contact: Search Committee, Director, Student Health Center, c/o Dean of Student Affairs Office, Sonoma State University, Rohnert Park, CA 94928; (707) 664-2838. Salary Range: $62,000 to $82,000 annually. Applications must be received no later than March 13, 1987. AA/EO Employer.

(Continued on Page 272)

THE PROBLEM

Most physicians today are falling short of their personal financial goals. Competitive pressures from a growing number of providers and from aggressive HMO's have resulted in a decline in the average physician net income.

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- Develop internal and external marketing strategies to both generate and retain patients.
- Design a wide range of personal financial plans and strategies to minimize tax liabilities and investment risk, and maximize personal income and satisfaction.

THE COMPANY

Medical Office Consultants is a group of professionals with extensive background in medical office management, accounting, banking, legal, health care marketing, insurance and real estate. We would like to demonstrate to you our ability to problem solve, identify opportunities and implement strategies benefiting your practice and you, personally.

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(Continued from Page 270)

PHYSICIANS WANTED

SANTA BARBARA—Santa Barbara County Health Care Services position available for Deputy Director, Public Health Services. Reporting directly to the Agency Director, this executive position is responsible for overall functioning of Public Health Services. Requires valid California license as a physician and surgeon and five years public health administrative experience or three years public health experience and two years clinical. Prefer person with strong leadership, planning, organizational, and staff development skills to coordinate administrative and medical programs and personnel. Salary $81,468/year plus excellent benefits including $3,020 management benefits. Open until filled. Obtain County application and supplemental questionnaire from: Santa Barbara County Personnel Department, 1226 Anacapa St., Santa Barbara, CA 93101; (805) 963-7155. AA/EOE.

FAMILY PRACTICE PHYSICIAN: Immediate opportunity available for board certified physician to establish own practice in rural community of central Arizona. Clinic facility and equipment available. Center is located 15 minutes from scenic Sedona, Arizona and 1 hour from Flagstaff, Arizona. Financial arrangements include 1 year's rent and some startup costs. Great growth potential. Affiliated with Marcus J. Lawrence Memorial Hospital in Cottonwood, Arizona. Reply: Peggy A. Broussard, AHPR, 3131 E. Second St., Tucson, AZ 85716; (602) 626-7946.

PRACTICES AVAILABLE

FOR SALE—Well established internal medicine practice. Two offices—Los Angeles and Beverly Hills. Gross $300,000 plus. $100,000 down and additional $25,000/year for 4 years. Qualified buyers only. Please reply to Number 144, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

DERMATOLOGY: Multiple practice situation. Long established. Prime Orange County California location. High volume, large gross. Particulars negotiable. Relpy to Number 3, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FOR SALE: INTERNAL MEDICINE PRACTICE. Established successful next to hospital with ICU/CCU. Nearby Ventura County Medical Center with UCLA affiliation. Resort town. Includes equipment, furniture, supplies, assumable lease and trained personnel. Annual gross 225K. Call (805) 646-0126 or (812) 473-3101.

GENERAL PRACTITIONER retiring after 27 years in a practice serving the San Francisco Chinese community. Located in the center of Chinatown, practice may be purchased with all equipment and accounts receivable. If interested call Dr Ed Liu, (415) 731-7737.

WASHINGTON—Located in Bellevue, a suburb of Seattle. Retiring from a family practice of 24 years. 99% collection history. Fully equipped office in growth area. Terms negotiable for a very reasonable price. Inquire PO Box 792, Bellevue, WA 98009.

PALM SPRINGS AREA—Active medical practice. No OB, Ped, Surg. Two hospitals opened to qualified MD—year-round golf, tennis, sunshine. Gross near 200K for 24 hr/week. Potential unlimited for aggressive MD. $25,000 down and easy terms. Excellent lease. Reply to Number 7, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA: Practices for Sale or Positions Available: Neurosurgery, Dermatology, Family/General, Ophthalmology, Gastroenterology, Surgery, Occupational Medicine, OB/GYN, Pediatrics, Internal, Hematology/Oncology, Allergy, Orthopedics, Otolaryngology, Psychiatry, Pulmonary, Radiology, Rheumatology, Urology plus many others. Mary Bradshaw, Practice Broker/Recruiter, Valuations, 21 Altamount Dr., Orinda, CA 94563, (415) 376-0762.

PRACTICES AVAILABLE

PARTNERSHIP SHARE in a multispecialty Medical Clinic and the first spa-hotel and restaurant built for patients and their companions in the State of California. The desert health resort city has natural hot mineral water and a dry and warm climate. The applicant should have an interest and experience in Internal Medicine, Geriatrics, arthritis, Physical Medicine or clinic administration. Located 100 miles east of Los Angeles and 15 miles north of Palm Springs. Write to: Desert Arthritis and Medical Clinic, PO Box 866, Desert Hot Springs, CA 92240.

FOR SALE: SAN MATEO, CALIFORNIA. Established General Practice—retiring. Accounts, equipment, furniture. Terms. Reply to Number 2, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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SITUATION WANTED

BOARD CERTIFIED INTERNIST, age 60, desires part-time outpatient work. San Francisco Bay area. Excellent background and references. Please reply to Number 8, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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INSURANCE? We have some options. Umbrella or self-insure. For details write, McBride Agency, PO Box 18039, Orlando, FL 32860.

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FOR SALE: Siemens Lem Portable Gamma Camera, high resolution, thin crystal, Microdot Imager, $35,000 or assume $650 lease payment. Also for sale: Siemens Pho-Gamma HP Gamma Camera with 37 tube upgrade and thin crystal with all collimators. Hasselblad imaging system. $12,500. Please call (602) 258-3484.

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WANTED: Physician to share 2,500 sq. ft. new, beautifully decorated, first floor medical suite. Parkwood Medical Building, 5501 W. 19th Ave., Phoenix, AZ 85015; (602) 242-7933.

OFFICE FOR SALE—1,200 square feet located in Doctor's Village Medical Complex in beautiful Flagstaff, Arizona. This office is located within 2 blocks of the Flagstaff Medical Center and is perfect for a one man practice. Call (602) 779-5335, 9 am to 4 pm. Dr Michael J. Keberlein, 1360 North Rim Dr., Flagstaff, AZ 86001.

SAN FRANCISCO. Across from Mt. Zion Hospital. 395, 765 and 1,400 sq. ft. Established medical building in desirable area.
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SEMINARS

THE AMERICAN ASSOCIATION OF ORTHOPAEDIC MEDICINE presents "Diagnostic Models of Musculoskeletal Pain," May 12-17, 1987, Montreal, Canada. Contact: Deborah Staller, Exec. Sec., AAOM, 926 E. McDowell Rd., Ste 202, Phoenix, AZ 85006; (602) 254-5315.

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(Continued from Page 258)

February 20-21—**Office Gynecology for the Primary Care Physician.** Seattle. Fri-Sat. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Health and Safety of Firefighters.** Seattle. Thurs-Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

March 6-7—**Primary Care Orthopedics.** Seattle. Fri-Sat. Contact: U/W.

March 6-7—**Update in Internal Medicine 1987.** Spokane. Fri-Sat. Inn at the Park. Contact: Howard M. Kenney, MD, South Center Medical Bldg, Spokane 99204. (509) 838-6500

March 13—**Recent Developments in Occupational Medicine.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

March 13—**Anxiety/New Research Findings for the Clinician.** Seattle. Fri. U/W Health Sciences. Contact:U/W.

March 18—**New Directions in Gynecologic Research.** Seattle. Wed. U/W Health Sciences. Contact: U/W.

March 20—**Neuro-Opthalmology Seminar.** Seattle. Fri. Virginia Mason Medical Center. Contact: VMMC.

March 30-April 10—**Rehabilitation Medical Review.** Seattle. Mon-Fri. Stouffer Madison Hotel. Contact: U/W.

April 15-16 —**Introduction to Industrial Hygiene.** Seattle. Wed-Thurs. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 17—**Basic Monitoring Laboratory.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 25—**Mason Clinic Day.** Seattle. Sat. Virginia Mason Medical Center. Contact: VMMC.

May 1—**Topics in Pulmonary Medicine: Obstructive Airflow Disease Treatment.** Seattle. Fri. Virginia Mason Medical Center. Contact: VMMC.

May 8—**Current Issues in Asbestos Control.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

May 14-15—**Clinical Microbiology.** Seattle. Thurs-Fri. Contact: U/W.

May 20—**Management of Benign and Malignant Breast Disease.** Seattle. Wed. U/W Health Sciences. Contact: U/W.

May 28-29—**Workers Compensation Update.** Seattle. Thurs-Fri. NW Center for Occupational Health and Safety. Contact U/W.

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Pediatric Use: Safety and effectiveness in children below the age of 4 years have not been established.

ADVERSE REACTIONS: The most frequently reported adverse reaction attributed to the use of OPTICROM, on the basis of reoccurrence following readministration, is transient ocular stinging or burning upon instillation.

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CAUTION: Federal law prohibits dispensing without prescription.

REFERENCE: 1. Allansmith MR, Abelson MB. Ocular Allergies. In: *The Cornea*, ed. by G. Smolin, RA Thoft, Little, Brown and Co., Boston/Toronto, 1983: 231-43.

See package insert for full prescribing information.

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1987: Date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1987: Date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Interim Meeting: April 3-4, 1987, Colonial Inn, Helena.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 3-4, 1987, Salishan Lodge, Lincoln City.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1987: Date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1987: Date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

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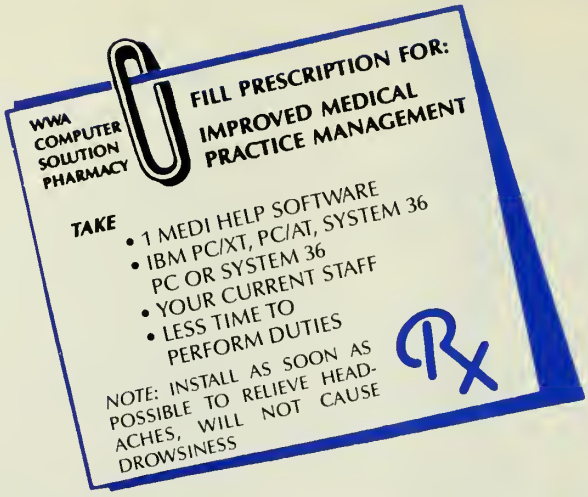

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Before prescribing, please consult complete product information, a summary of which follows:

MICROBIOLOGY The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

GRAM-NEGATIVE AEROBES *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neissena gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neissena meningitidis, Proteus mirabilis, Proteus vulgans, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, e g, penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

GRAM-POSITIVE AEROBES *Staphylococcus aureus* (including penicillinase-producing strains) and *Staphylococcus epidermidis* (Note methicillin resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

GRAM-NEGATIVE AEROBES *Citrobacter freundii, Citrobacter diversus, Providencia* species (including *Providencia rettgen*), *Salmonella* species (including S *typhi*), *Shigella* species and *Acinetobacter calcoaceticus*

ANAEROBES *Bacteroides* species, *Clostridium* species (Note most strains of *C difficile* are resistant)

SUSCEPTIBILITY TESTING Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW Kirby WMM, Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45 493-496, 1966, Standardized Disk Susceptibility Test, *Federal Register* 39 19182-19184 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g, urine), in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

DILUTION TECHNIQUES Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g, urine), in which high antibiotic levels are attained

E coli ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgans, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neissena gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

PROPHYLAXIS The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

ROCEPHIN® (ceftriaxone sodium/Roche)

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed *no* potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are, however, no adequate and well controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone *no* adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after IV administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia neutropenia lymphopenia thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia palpitations and epistaxis

DOSAGE AND ADMINISTRATION Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams) given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g, dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

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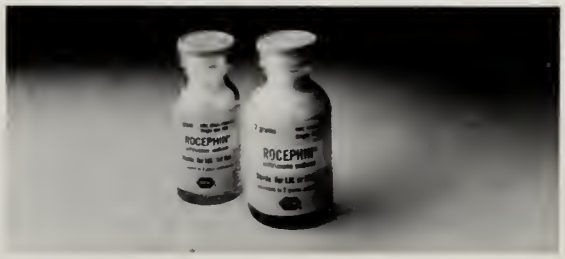

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3. Richards DM, *et al: Drugs 27*:469-527, 1984.
4. Cleeland R, Squires E: *Am J Med 77*:3-11, Oct 19, 1984.
5. Tanner DJ, Nazarian MQ: *Am J Med 77*:104-111, Oct 19, 1984.

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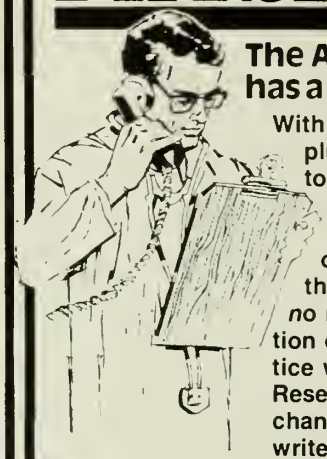

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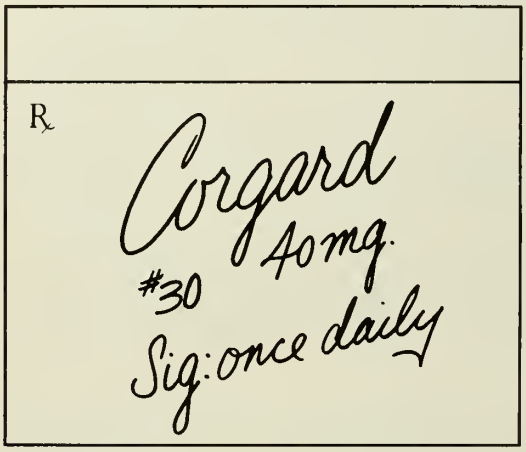

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Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect, monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**— fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and in Unimatic® unit-dose packs of 100 tablets. The 40 mg, 80 mg, and 120 mg potencies are also available in bottles of 1000 tablets. (J3-527E)

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The Western Journal of Medicine

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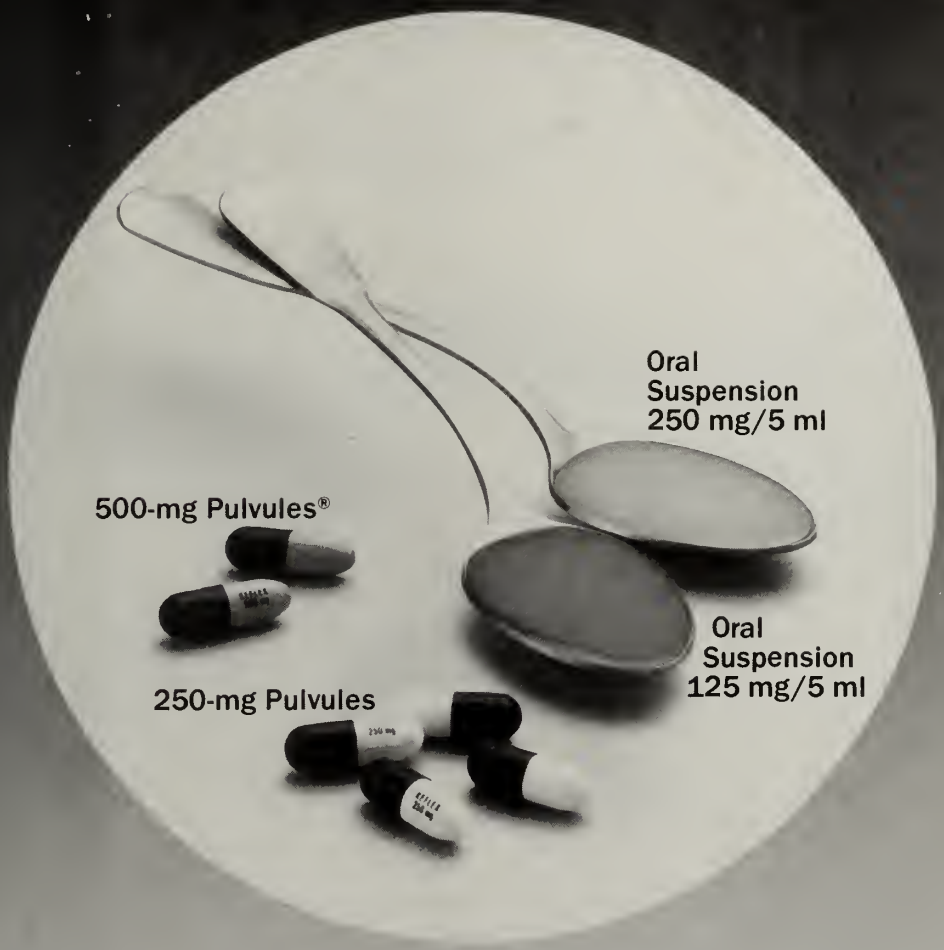

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(ibuprofen)

CONTRAINDICATIONS: Anaphylactoid reactions have occurred in individuals hypersensitive to MOTRIN or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

WARNINGS: Peptic ulceration and G.I. bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use MOTRIN under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If MOTRIN is used, observe the patient closely for signs of ulcer perforation or G.I. bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue MOTRIN and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with MOTRIN, use with caution in patients with a history of cardiac decompensation or hypertension.

MOTRIN can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision, skin rash, weight gain, or edema.

Patients on prolonged corticosteroid therapy should have therapy tapered slowly when MOTRIN is added.

The antipyretic, anti-inflammatory activity of MOTRIN may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), MOTRIN should be discontinued.

In cross-study comparisons with 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. The total decrease in hemoglobin usually does not exceed 1 gram.

Renal Effects: Long term administration of ibuprofen and other NSAID's to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. In patients with prerenal conditions and reduced renal blood flow or blood volume, NSAID's may precipitate overt renal decompensation. Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly are at greatest risk. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

In patients with renal impairment, reduced dosage may be necessary. Prospective studies of MOTRIN safety in patients with chronic renal failure have not been done.

Drug Interactions: Aspirin: Used concomitantly may decrease MOTRIN blood levels.

Coumarin: Bleeding has been reported in patients taking MOTRIN and coumarin.

Pregnancy and nursing mothers: MOTRIN should not be taken during pregnancy or by nursing mothers.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with MOTRIN is gastrointestinal of which one or more occurred in 4% to 16% of the patients. Reported side effects were higher at 3200 than at 2400 mg/day or less.

Incidence Greater than 1% (but less than 3%) – Probable Causal Relationship

GASTROINTESTINAL: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **CENTRAL NERVOUS SYSTEM:** Dizziness,* headache, nervousness; **DERMATOLOGIC:** Rash* (including maculopapular type), pruritus; **SPECIAL SENSES:** Tinnitus; **METABOLIC/ENDOCRINE:** Decreased appetite; **CARDIOVASCULAR:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1% Probable Causal Relationship*

GASTROINTESTINAL: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **CENTRAL NERVOUS SYSTEM:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **DERMATOLOGIC:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **SPECIAL SENSES:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS); **HEMATOLOGIC:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS); **CARDIOVASCULAR:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **ALLERGIC:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **RENAL:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **MISCELLANEOUS:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1% – Causal Relationship Unknown*

GASTROINTESTINAL: Pancreatitis; **CENTRAL NERVOUS SYSTEM:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **DERMATOLOGIC:** Toxic epidermal necrolysis, photoallergic skin reactions; **SPECIAL SENSES:** Conjunctivitis, diplopia, optic neuritis, cataracts; **HEMATOLOGIC:** Bleeding episodes (e.g. epistaxis, menorrhagia); **METABOLIC/ENDOCRINE:** Gynecomastia, hypoglycemic reaction, acidosis; **CARDIOVASCULAR:** Arrhythmias (sinus tachycardia, sinus bradycardia); **ALLERGIC:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema; **RENAL:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with MOTRIN. (Those reactions occurring in less than 3% of the patients are unmarked).

Reactions are classified under **"Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under **"Causal Relationship Unknown"** if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

DOSAGE AND ADMINISTRATION: Do not exceed 3200 mg/day.

Rheumatoid and osteoarthritis: Suggested dosage is 1200 to 3200 mg per day (400, 600 or 800 mg t.i.d. or q.i.d.). The smallest effective dosage should be used. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

HOW SUPPLIED:

MOTRIN Tablets, 400 mg (orange)	MOTRIN Tablets, 600 mg (peach)	MOTRIN Tablets, 800 mg (apricot)
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February 1986
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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

RENAL AND UROLOGIC EMERGENCIES—Volume 8 in Clinics in Emergency Medicine—Edited by Allan B. Wolfson, MD, Assistant Professor, Department of Medicine, University of Pennsylvania School of Medicine, and Associate Director, Emergency Services Department, Hospital of the University of Pennsylvania, Philadelphia, and Ann Harwood-Nuss, MD, Associate Professor, Division of Emergency Medicine, Department of Surgery, University of Florida College of Medicine, Gainesville, and University Hospital, Jacksonville. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 282 pages, $35.

RENAL TRANSPLANTATION—Edited by Marvin R. Garovoy, MD, Associate Professor of Surgery and Medicine, University of California, San Francisco, School of Medicine, and Director, Immunogenetic and Transplantation Laboratory, The Medical Center at the University of California, San Francisco, and Ronald D. Guttmann, MD, Professor of Medicine, McGill University Faculty of Medicine, and Director, Transplantation Service, Royal Victoria Hospital, Montreal. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 435 pages, $59.

REPRODUCTIVE FAILURE—Edited by Alan H. DeCherney, MD, John Slade Ely Professor of Obstetrics and Gynecology, and Director, Division of Reproductive Endocrinology, Yale University School of Medicine, New Haven, Connecticut. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 302 pages, $45.

REPRODUCTIVE PROBLEMS IN THE WORKPLACE—Edited by Zena A. Stein, MA, MB, BCh, Director, Epidemiology of Brain Disorders, Research Department, New York State Psychiatric Institute, and Professor of Public Health (Epidemiology), Columbia University, and Maureen C. Hatch, PhD, Assistant Professor of Public Health (Epidemiology), Columbia University School of Public Health, New York. Hanley & Belfus, Inc, 210 S 13th St, Philadelphia, PA 19107, 1986. 534 pages, $26.

RESPIRATORY INFECTIONS—Volume I in Contemporary Issues in Infectious Diseases—Edited by Merle A. Sande, MD, Professor and Vice Chairman, Department of Medicine, University of California, San Francisco, School of Medicine, and Chief, Medical Service, San Francisco General Hospital; Leonard D. Hudson, MD, Professor of Medicine and Head, Respiratory Diseases Division, Harborview Medical Center, Seattle, and Richard K. Root, MD, Professor and Chairman, Department of Medicine, University of California, San Francisco, School of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 361 pages, $47.

RETINOBLASTOMA—Volume 2 in CONTEMPORARY ISSUES IN OPHTHALMOLOGY—Edited by Frederick C. Blodi, MD, Director, Medical Education, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 223 pages, $45.

SHOCK TRAUMA/CRITICAL CARE MANUAL—Initial Assessment and Management—Edited by R. Adams Cowley, MD, Director, and C. Michael Dunham, MD, Attending Traumatologist, Maryland Institute for Emergency Medical Services Systems, Baltimore. University Park Press, 300 N Charles St, Baltimore, MD 21201, 1982. 586 pages, price not given.

SIXTEENTH CENTURY PHYSICIAN AND HIS METHODS—MERCURIALIS ON DISEASES OF THE SKIN—THE FIRST BOOK ON THE SUBJECT (1572)—Translation from the Latin, glossary and commentary by Richard L. Sutton, Jr, MD, ScD, FRS Edin, Emeritus Clinical Professor, Dermatology, University of Kansas, and Adjunct Professor, Medicine, Ophthalmology and Geosciences, University of Missouri, Kansas City. Lowell Press Inc, 115 E 31st St, PO Box 1877, Kansas City, MO 64141, 1986. 226 pages, $37.50.

STAGING OF NEOPLASMS—Volume 7 in CONTEMPORARY ISSUES IN COMPUTED TOMOGRAPHY—Edited by Gary M. Glazer, MD, Associate Professor of Radiology and Director, Divisions of Body Computed Tomography and Magnetic Resonance Imaging, University of Michigan Medical School, Ann Arbor. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 299 pages, $39.

STRAINED MERCY—THE ECONOMICS OF CANADIAN HEALTH CARE—Robert G. Evans, Professor of Economics, University of British Columbia, Vancouver. Butterworth Legal Publishers, Western Region, Redmond, WA 98052, 1984. 380 pages, price not given.

STROKE: PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT—2 volumes—Edited by Henry J. M. Barnett, OC, MD, FRCP(C), FRCP, Professor of Neurology, Department of Clinical Neurological Sciences, University of Western Ontario, University Hospital, and Scientific Director, John P. Robarts Research Institute, London, Ontario, Canada; J. P. Mohr, MD, Sciarra Professor of Clinical Neurology, College of Physicians and Surgeons of Columbia University, and Director of Cerebrovascular Research, The Neurological Institute of New York, Columbia Presbyterian Medical Center, and Bennett M. Stein, MD, Byron Stookey Professor of Neurological Surgery, College of Physicians and Surgeons of Columbia University, and Director of Neurological Surgery, The Neurological Institute of New York, Columbia Presbyterian Medical Center, New York, and Frank M. Yatsu, MD, Professor and Chairman of Neurology, University of Texas Health Science Center at Houston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 1,274 pages, $159.

TEXTBOOK OF GENITO-URINARY SURGERY—2 Volumes—Edited by Hugh N. Whitfield, MA, MChir, FRCS, Consultant Urological Surgeon. St Bartholomew's Hospital, Hackney Hospital and St Mark's Hospital for Diseases of the Rectum and Colon, and Honorary Consultant Urologist, St Luke's Hospital for the Clergy, and William F. Hendry, ChM, FRCS, FRCS(Ed), Consultant Genito-urinary Surgeon, St Bartholomew's Hospital, Royal Marsden Hospital and Chelsea Hospital for Women; Honorary Senior Lecturer, Institute of Urology, and Civilian Consultant in Urology to the Royal Navy, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1985. 1,396 pages, $208.

TICS AND RELATED DISORDERS—Volume 7 in CLINICAL NEUROLOGY AND NEUROSURGERY MONOGRAPHS—A. J. Lees, MD, MRCP, Consultant Neurologist, National Hospitals for Nervous Diseases, University College Hospital and Whittington Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1986. 269 pages, $45.

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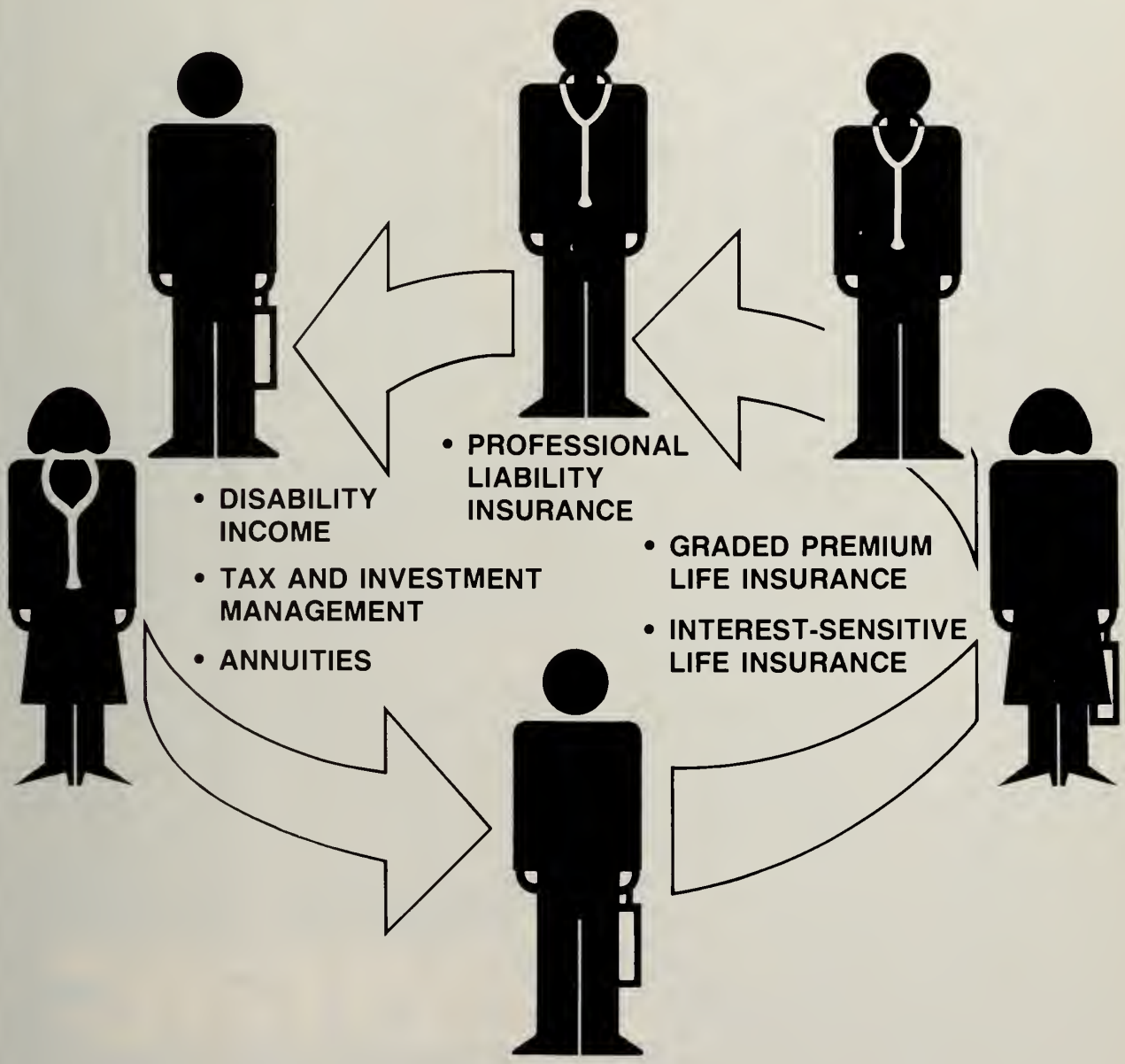

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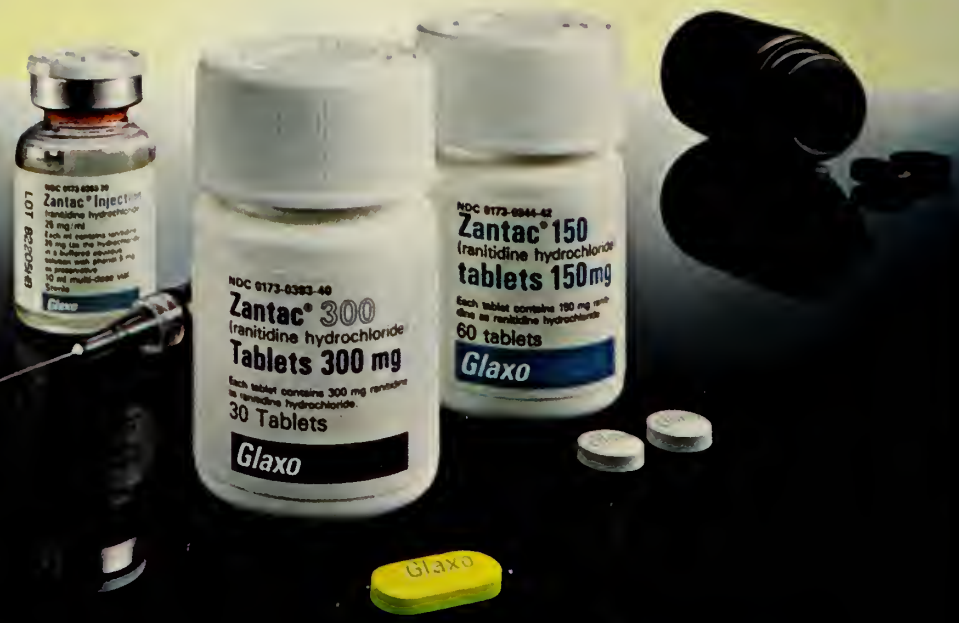

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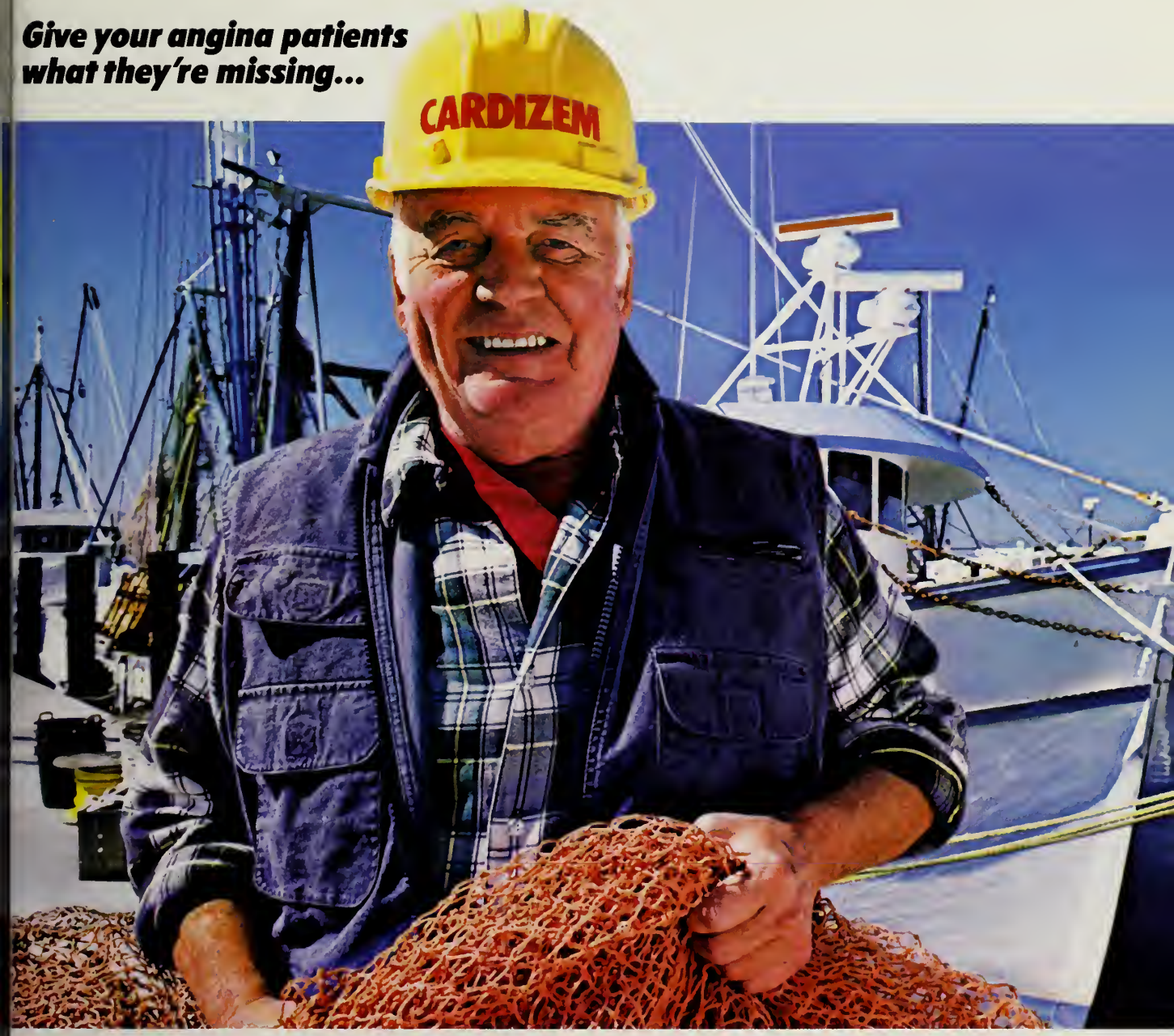

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Please see brief summary of prescribing information on the next page.

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60 mg tid or qid

Brief Summary
Professional Use Information

CARDIZEM®
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CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt).
   Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System:	Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other	Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 7/86

See complete Professional Use Information before prescribing.

References: 1. Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983, 106(6):1341-1347. **2.** Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984,24(Dec):150-159. **3.** Johnston DL, Lesowoy R, Human DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris. A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985,55:680-687. **4.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **5.** Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982,50(Sept):94-116.

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CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**)
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block, significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg, or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, arterial insufficiency, usually of the Raynaud type, palpitations, congestive heart failure, peripheral edema, and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 17-20—**Pediatric Update—1987.** La Posada Resort, Scottsdale. Tues-Fri. Contact: Phoenix Children's Hospital, (602) 239-4350.

March 19-21—**23rd Annual Arizona Chest Symposium.** Doubletree Hotel, Tucson. Thurs-Sat. Contact: Sandy Younker-Hellman, RN, U of A, (602) 327-5461.

March 19-21—**Gastroenterology for Clinicians.** Scottsdale. Thurs-Sat. Contact: Jeanne Sun Harris, 4129 E Sandy Mt Rd, Scottsdale 85253.

March 21-22—**13th Annual James H. McDonald Urological Seminar.** Sheraton Scottsdale Resort, Scottsdale. Sat-Sun. Contact: Maricopa Medical Center, (602) 267-5371.

March 31-April 3—**12th Annual Update: Primary Care.** Arizona Health Sciences Center, Tucson. Tues-Fri. Contact: U of A.

April 6-8—**Practical Cardiology for the Family Physician.** La Posada Resort, Scottsdale. Mon-Wed. Contact: American College of Cardiology, (301) 897-5400, ext 226.

April 22—**Current Perspectives: Wellness.** Arizona Medical Association, Phoenix. Wed. Contact: ArMA.

April 23—**Current Perspectives: Wellness.** VA Medical Center, Prescott. Thurs. Contact: ArMA.

April 24—**Clinical Aspect of Aging.** Fri. Contact: Dr Stonefeld, (602) 230-3479.

May 9-10—**Pathology of AIDS.** Loews Ventana Canyon Resort, Tucson. Sat-Sun. Contact: Beverly Richter for Arizona Society of Pathologists, (602) 246-8901.

June 4—**Arizona Medical Association Annual Scientific Session.** The Pointe at South Mountain, Phoenix. Thurs. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

March 18-21—**10th Annual Course: Frontiers in Allergy and Asthma—A Comprehensive Update for the Treatment of Allergy/Asthma Patients.** UCD at Embassy Suites, Napa Valley. Wed-Sat. 17 hrs. $225. Contact: UCD.

ANESTHESIOLOGY

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Fri-Sun. Contact: UCSF.

March 21-22—**Los Angeles County Society of Anesthesiologists 32nd Postgraduate Assembly.** Los Angeles Hilton Hotel. Sat-Sun. Contact: LA County Society of Anesthesiologists, 333 S Beverly Dr, Ste 111, Beverly Hills 90212. (213) 556-8865.

April 26-May 1—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Kauai Hotel, Poipu Beach, Hawaii. Sun-Fri. 21 hrs. $375. Contact: Linda P. Londerville, CSA, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

May 1-3—**Clinical Neuromuscular Pharmacology—1987.** Anesthesiology Educational Foundation and UCLA at Palm Springs. Fri-Sun. 15 hrs. Contact: Anesthesiology Educational Foundation, PO Box 24230, Federal Bldg, Los Angeles 90024. (213) 825-0736.

June 25-28—**California Society of Anesthesiologists Annual Meeting.** Hotel Inter-Continental, San Diego. Thurs-Sun. 15 hrs. $225. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

August 23-28—**California Society of Anesthesiologists Hawaiian Seminar.** Sheraton Royal Waikoloa Hotel, The Big Island, Hawaii. Sun-Fri. 20 hrs. $375. Contact: Linda P. Londerville, 100 S Ellsworth Ave, Ste 806, San Mateo 94401. (415) 348-1407.

CANCER

March 18-20—**7th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 18 hrs. $275-325. Contact: UCSF

April 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Fri. 7 hrs. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Newporter Hotel, Newport Beach. Sun. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 1—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Vacation Village Resort, San Diego. Fri. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

May 3—**1 Day Colon Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sun. $175. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 299)

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(Continued from Page 297)

CARDIOLOGY

March 22-25—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Royal Lahaina Hotel, Maui, Hawaii. Sun-Wed. 13 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

March 27-28—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Desert Inn Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 9-11—**State of the Art Cardiology: The Excitement of the 80s.** Pacific Presbyterian Medical Ctr, San Francisco. Thurs-Sat. Contact: Pacific Presbyterian Med Ctr, Continuing Education, PO Box 7999, San Francisco 94120. (415) 923-3440.

April 10-11—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Inter-Continental Hotel, San Diego. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

April 27-May 6—**Cardiology for the Consultant.** Scripps Clinic and Research Foundation at Rancho Santa Fe Inn, Rancho Santa Fe. Mon-Wed. 40 hrs. $800. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 1-2—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Bally's (MGM) Grand Hotel, Las Vegas, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or in CO 798-9682.

May 24-30—**5th Annual Cardiology Update.** Institute for Medical Studies at Honolulu, Hawaii. Sun-Sat. 26 hrs. $395. Contact: Lisa Krehbiel, Inst for Med Studies, 30131 Town Ctr Dr, Ste 215, Laguna Niguel 92677. (714) 495-4499.

June 7-10—**Critical Examination Review Course.** American College of Chest Physicians at Hotel Del Coronado, Coronado. Sun-Wed. 30 hrs. $575. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (312) 698-2200.

June 10—**Cardiology: Arrhythmias.** LLU at LLU. Wed. 4 hrs. $60. Contact: LLU.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 18-20—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Waikiki Hotel, Honolulu, Hawaii. Thurs-Sat. 11 hrs. $295. Contact: Debbie Wilderson, Medical Education Resources, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

June 25-27—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Hotel, Costa Mesa. Thurs-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

July 17-18—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Sheraton Hotel, Anaheim. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

July 31-August 1—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Harvey's Hotel, Lake Tahoe, Nevada. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 7-8—**Coronary Heart Disease: Current Concepts.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sat. 11 hrs. $295. Contact: Debbie Wilderson, 5808 S Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756 or (303) 798-9682.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

DERMATOLOGY

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

August 13-15—**Problems of the Aging Skin.** STAN at Hyatt Rickeys Hotel, Palo Alto. Thurs-Sat. Contact: STAN.

August 14-15—**Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, Director, 412 W Carroll, Glendora 91740. (818) 963-7684.

EMERGENCY MEDICINE

March 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

April 11-18—**Infectious and Toxicologic Emergencies.** Scripps Memorial Hospital, Encinitas at Waiohai Resort and Poipu Beach Hotel, Kauai, HI. One week. 21 hrs. $375. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

April 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

April 25-May 1—**Critical Care Medicine.** University of Colorado at Inter-Continental Hotel, Maui, Hawaii. Sat-Fri. 20 hrs. $395. Contact: Univ of CO, Office of CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. (303) 394-5195.

May 4-8—**Postgraduate Institute for Emergency and Primary Care Physicians—Symposium I and Advanced Emergency Procedures Laboratory.** UCSD at Hotel Inter-Continental, San Diego. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

(Continued on Page 302)

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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

CONTINUING MEDICAL EDUCATION

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May 13-17—**9th Annual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

June 1-5—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

June 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III and Advanced Emergency Procedures Lab.** UCSD at Hanalei Hotel, San Diego. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

July 24-26—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Franicsco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 17-21—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II and Advanced Emergency Procedures Lab.** UCSD at UCSD. Mon-Fri. 32 hrs. $325-440. Contact: UCSD.

INTERNAL MEDICINE

March 20-21—**Update in Gastroenterology—1987.** Eisenhower Medical Center, Rancho Mirage. Fri-Sat. Contact: Annenberg Ctr for Health Sciences, Eisenhower Med Ctr, 39000 Bob Hope Dr, Rancho Mirage 92270. In California, (800) 621-7322, National, (800) 321-3690.

March 30-April 1—**Federation of Western Societies of Neurological Science 24th Annual Meeting.** Mon-Wed at Hotel Del Coronado, Coronado. Contact: Patrick D. Lyden, MD, Dept of Neurosciences, UCSD Medical Center H-815A, 225 W Dickinson St, San Diego 92103. (619) 452-3940.

April 2-4—**Intrauterine Diagnosis and Treatment: The New Frontier.** UCSD at Hotel Inter-Continental, San Diego. Thurs-Sat. Contact: UCSD.

April 4-5—**Diabetes Update: 2nd Triennial Conference.** Cypress Foundation at Hyatt Regency, Monterey. Sat-Sun. 10 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

April 8-10—**Advances in Infectious Disease: Current Therapy.** UCSF at Hyatt Regency Embarcadero, San Francisco. Wed-Fri. 16 hrs. $350. Contact: UCSF.

April 23-24—**7th Annual Infectious Diseases—Clinical Update.** Sutter Community Hospitals and Mercy Hospital of Sacramento at Red Lion Inn, Sacramento. Thurs-Fri. 14 hrs. Contact: Infectious Diseases Symposium, Metro Centre, 1600 Sacramento Inn Way, Ste 132, Sacramento 95815. (916) 925-1366.

April 29—**Thyroid '87.** Hospital of the Good Samaritan at Moseley-Salvatori Conference Ctr, Los Angeles. Wed. 7 Hrs. Contact: Dolores Gay, Hosp of the Good Samaritan, 637 S Lucas Ave, Los Angeles 90017. (213) 977-2555.

May 2—**New Treatments in Liver and Biliary Tract Disease.** Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

May 16—**Clinical Aspects of Viral Disease.** Grossmont District Hospital at Kona Kai Club, San Diego. Sat. Contact: Vera Belyeu, Grossmont District Hospital, 5555 Grossmont Center Dr, La Mesa 92041. (619) 465-0711, ext 245.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Mon-Fri. 32 hrs. $440. Contact: UCSF.

June 17-19—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Hyatt on Union Square, San Francisco. Wed-Fri. 17 hrs. $375. Contact: UCSF.

June 22-26—**Advances in Internal Medicine.** UCSF at UCSF. Mon-Fri. 32 hrs. $440.

June 26—**New Developments in Gastroenterology: Mucosal Injury, Esophageal Reflux and Sleep Disorders.** Sequoia Hospital and the Northern California Society for Clinical Gastroenterology at San Francisco Airport Hilton Hotel. 6 hrs. Contact: Daniel Liebowitz, MD, Sequoia Hospital, (800) 345-0409.

OB/GYN

March 20-22—**Obstetrical Anesthesia—1987.** UCSF at Hotel Meridien, San Francisco. Fri-Sun. Contact: UCSF.

March 25-28—**Gynecological Surgery With Emphasis on Vulvar and Vaginal Disease.** UCI at Hilton Riviera, Palm Springs. Wed-Sat. 16.5 hrs. Contact: UCI.

April 2-4—**Fetal Diagnosis and Treatment.** UCSD. Thurs-Sat. Contact: UCSD.

April 30-May 2—**12th Annual Symposium: Care of the Sick Newborn.** UCI. Thurs-Sat. 19 hrs. Contact: UCI.

May 6-10—**Annual Scientific Program and Postgraduate Courses.** Pacific Coast Fertility Society at Americana Canyon Hotel, Palm Springs. Wed-Sun. 22 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

May 7-8—**Advanced Fetal Rate Monitoring.** UCI. Thurs-Fri. Contact: UCI.

June 11-13—**Gynecologic Oncology and Breast Disease.** American College of Obstetricians and Gynecologists at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave, SW, Washington, DC 20024-2588. (202) 638-5577.

June 30-July 5—**5th Annual Controversies in Obstetrics and Gynecology.** UCI at Mauna Kea Beach Resort, Hawaii. Tues-Sun. 22 hrs. Contact: UCI.

ORTHOPAEDICS

April 3-5—**Techniques of Intramedullary Nailing: Tibia, Humerus, and Femur.** Centinela Hospital Medical Center at Century Plaza Hotel, Century City. Fri-Sun. 15 hrs. $395. Contact: Jeanne Spala, DME, Centinela Hospital, 555 E Hardy St, Inglewood 90307. (213) 673-4660, ext 8213.

April 30-May 2—**American Back Society Spring Symposium on Back Pain.** Anaheim Hilton Hotel. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, 2647 E 14th St, Oakland 94601. (415) 536-9929.

May 4-8—**Osteoporosis/Spine Update.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. Contact: UCSF.

PATHOLOGY

May 21-22—**Annual Meeting: Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Fri. 12 hrs. Contact: UCSF.

PEDIATRICS

April 2-4—**20th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

April 8—**Pediatrics: Genetics.** LLU. Wed. 4 hrs. $60. Contact: LLU.

April 10-11—**Ambulatory Pediatrics.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. 15 hrs. $175. Contact: UCD.

May 4-7—**Pediatrics in the 80s—The 17th Annual Pediatrics Course.** USC at Marina Beach Hotel, Marina del Rey. Mon-Thurs. 18.5 hrs. $395. Contact: USC—in California, (800) 321-1929, National, (800) 421-6729.

PSYCHIATRY

March 28-29—**The Cutting Edge 1987: Difficult Treatment Problems With Borderline and Narcissistic Patients.** UCSD at Hotel Inter-Continental, San Diego. Sat-Sun. 13 hrs. Contact: UCSD.

April 10-11—**Mental Health in the Workplace.** UCSF at Cathedral Hill Hotel, San Francisco. Fri-Sat. 11.5 hrs. $200. Contact: UCSF.

(Continued on Page 305)

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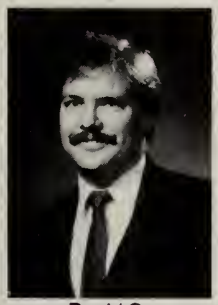

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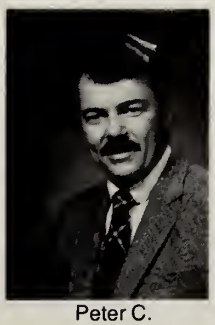

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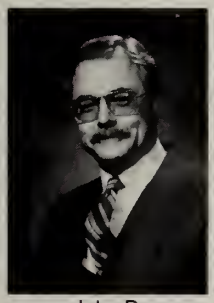

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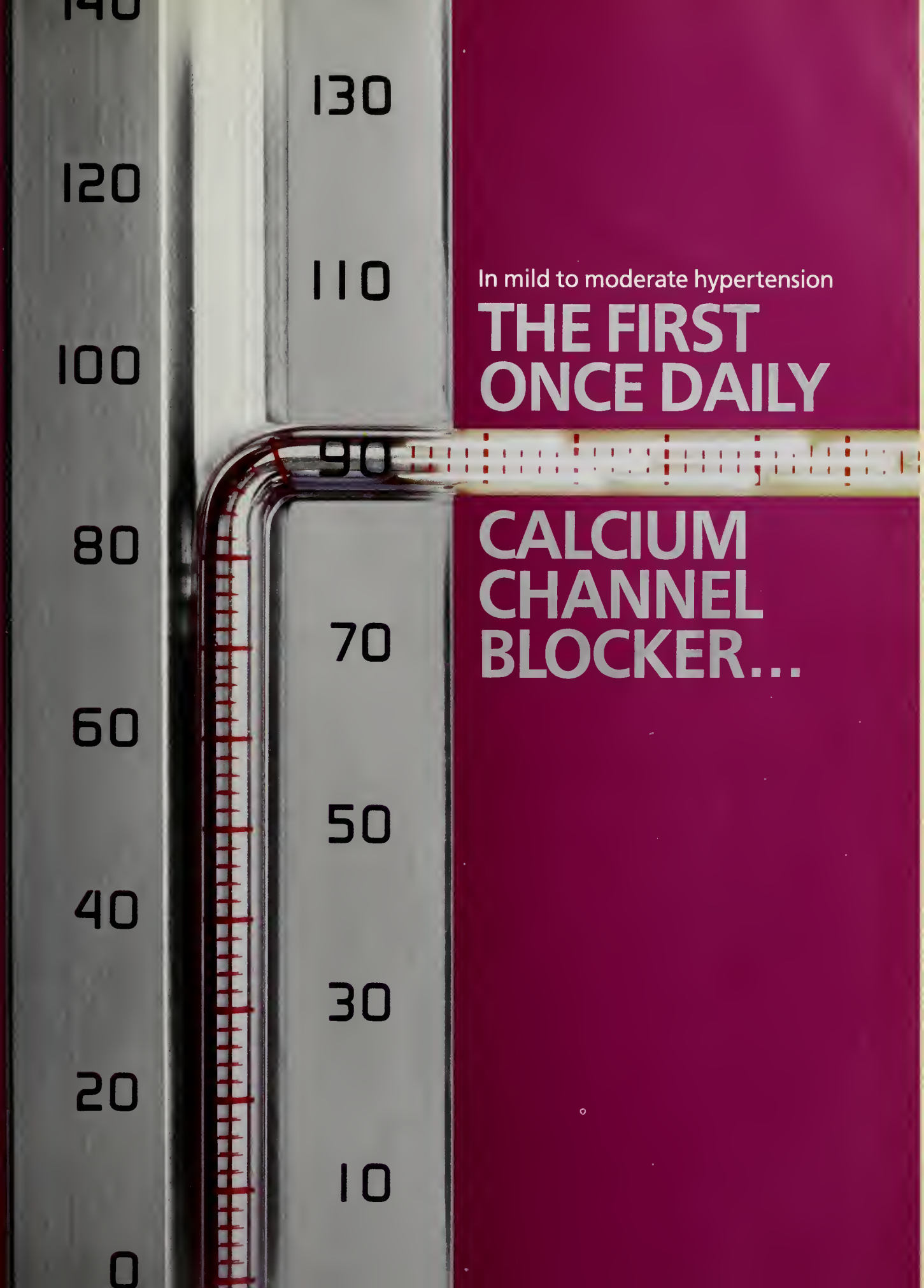
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JAMES B.
38, black male, heavy smoker. Prescribed a diuretic by another physician last year for hypertension.

YOUR CONCERNS
Presents with "smoker's cough." Workup reveals a BP of 150/107.

A LOGICAL CHOICE FOR CONTROL OF HIS BP
ISOPTIN* (verapamil HCl/Knoll) because...
— Black hypertensives often have low plasma renin activity and generally do not respond favorably to beta blockers.
— Beta blockers may increase the likelihood of bronchospasm.

ALICE W.
65, diabetic, overweight. Her BP has elevated to 190/98.

YOUR CONCERNS
She's on daily insulin.

A LOGICAL CHOICE FOR CONTROL OF HER BP
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike most beta blockers and diuretics, ISOPTIN has no adverse effects on serum glucose levels.
— Unlike most beta blockers, ISOPTIN does not mask the symptoms of hypoglycemia.

THOMAS G.
70, asthmatic. In the past, BP adequately controlled with 25 mg hydrochlorothiazide daily.

YOUR CONCERNS
Today patient presents with symptoms of gout. Workup reveals high uric acid level, low serum potassium, and BP elevated to 180/98.

A LOGICAL CHOICE FOR CONTROL OF HIS BP
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN will not decrease serum potassium levels or elevate uric acid levels.
— Unlike beta blockers, ISOPTIN can be used safely in asthma and COPD patients.

JOHN K.
42, Annual physical uncovered diastolic BP of 102... confirmed on three successive office visits. Unresponsive to nonpharmacologic intervention.

YOUR CONCERNS
Salesman, spends many hours of his working day in car... total cholesterol level 300, HDL 35.

A LOGICAL CHOICE FOR CONTROL OF HIS BP
ISOPTIN* (verapamil HCl/Knoll) because...
— Unlike diuretics, ISOPTIN does not cause urinary urgency.
— Unlike either beta blockers or diuretics, ISOPTIN will not adversely affect his already seriously compromised lipid profile.
— Unlike with propranolol, fatigue and impotence are rarely reported.

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In mild to moderate hypertension Brief Summary

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CONTRAINDICATIONS: 1) Severe left ventricular dysfunction (see WARNINGS), 2) Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock, 3) Sick sinus syndrome or 2nd or 3rd degree AV block (except in patients with a functioning artificial ventricular pacemaker).

WARNINGS: Heart Failure: ISOPTIN should be avoided in patients with severe left ventricular dysfunction (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled before verapamil treatment. Hypotension: ISOPTIN (verapamil HCl) may produce occasional symptomatic hypotension. Elevated Liver Enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. Accessory Bypass Tract (Wolff-Parkinson-White): Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. While this has not been reported with oral verapamil, it should be considered a potential risk. Treatment is usually D.C.-cardioversion. Atrioventricular Block: The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st degree AV block and transient bradycardia. Higher degrees of AV block, while infrequent (0.8%), may require a reduction in dosage or, in rare instances, discontinuation of verapamil HCl. Patients with Hypertrophic Cardiomyopathy (IHSS): Although verapamil has been used in the therapy of patients with IHSS, severe cardiovascular decompensation and death have been noted in this patient population.

PRECAUTIONS: Impaired Hepatic or Renal Function: Verapamil is highly metabolized by the liver with about 70% of an administered dose excreted in the urine. In patients with impaired hepatic or renal function verapamil should be administered cautiously and the patients monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects (see OVERDOSAGE).

Drug Interactions: Beta Blockers: Concomitant use of ISOPTIN and oral beta-adrenergic blocking agents may be beneficial in certain patients with chronic stable angina or hypertension, but available information is not sufficient to predict with confidence the effects of concurrent treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment increases serum digoxin levels by 50 to 75% during the first week of therapy and this can result in digitalis toxicity. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalization. Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers, prazosin) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Disopyramide: Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. Quinidine: In patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. There has been a report of increased quinidine levels during verapamil therapy. Nitrates: The pharmacologic profile of verapamil and nitrates as well as clinical experience suggest beneficial interactions. Cimetidine: Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination to 1/2. Anesthetic Agents: Verapamil may potentiate the activity of neuromuscular blocking agents and inhalation anesthetics. Carbamazepine: Verapamil may increase carbamazepine concentrations during combined therapy. Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability. Lithium: Verapamil may lower lithium levels in patient on chronic oral lithium therapy. Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of a carcinogenic potential of verapamil administered to rats for two years. Verapamil was not mutagenic in the Ames test. Studies in female rats did not show impaired fertility. Effects on male fertility have not been determined. Pregnancy (Category C): There are no adequate and well-controlled studies in pregnant women. ISOPTIN crosses the placental barrier and can be detected in umbilical vein blood at delivery. This drug should be used during pregnancy, labor, and delivery, only if clearly needed. Nursing Mothers: ISOPTIN is excreted in human milk, therefore, nursing should be discontinued while verapamil is administered. Pediatric Use: Safety and efficacy of ISOPTIN in children below the age of 18 years have not been established.

ADVERSE REACTIONS: Constipation 8.4%, dizziness 3.5%, nausea 2.7%, hypotension 2.5%, edema 2.1%, headache 1.9%, CHF/pulmonary edema 1.8%, fatigue 1.7%, bradycardia 1.4%, 3° AV block 0.8%, flushing 0.1%, elevated liver enzymes (see WARNINGS). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, arthralgia and rash, AV block, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, dyspnea, ecchymosis or bruising, equilibrium disorders, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, sweating, syncope, urticaria. Treatment of Acute Cardiovascular Adverse Reactions: Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE: Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 302)

RADIOLOGY

March 16-20—**Diagnostic Imaging—1987.** UCSF at Waiohai Hotel, Kauai, Hawaii. Mon-Fri. Contact: UCSF.

April 9-11—**Thoracic Imaging—1987.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

April 10-12—**OB/GYN and Abdominal Sonography: Update 1987.** UCSF at Hyatt Regency on Union Square, San Francisco. Fri-Sun. Contact: UCSF.

April 13-17—**Vascular Imaging.** University of Washington at Royal Lahaina Resort, Maui, Hawaii. Mon-Fri. Contact: Univ of Washington, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 19-25—**7th Annual San Diego Residents' Radiology Review Course.** UCSD at Town and Country Hotel, San Diego. Sun-Sat. Contact: UCSD.

May 1-3—**12 Annual Spring Diagnostic Ultrasound.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 19.5 hrs. $325. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

May 5-9—**7th Annual Diagnostic Ultrasound Post Conference Seminar.** Los Angeles Radiological Society at Sheraton Princeville Hotel, Kauai, Hawaii. Tues-Sat. 19 hrs. $395. Contact: Diane L. Johnson, LARS, 5200 Century Blvd, Ste 920, Los Angeles 90045. (213) 642-0921.

June 10-13—**Advanced Echocardiography and Doppler Ultrasound—1987.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wed-Sat. Contact: Mary Anne McInerny, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (301) 897-5400, ext 226.

June 14-16—**1987 Radiology US Open Golf Meeting.** UCSF at Hyatt Regency, San Francisco. Sun-Tues. Contact: UCSF.

August 13-15—**Advanced Ultrasound.** American College of Obstetricians and Gynecologists at Silverado Inn, Napa. Thurs-Sat. Contact: Robin Murray, ACOG, 600 Maryland Ave SW, Washington, DC 20024-2588. (202) 638-5577.

August 26-28—**Interventional Radiology.** UCSF at Hyatt Regency Hotel, San Francisco. Wed-Fri. Contact: UCSF.

SPORTS MEDICINE

March 16-20—**Annual University of Hawaii: Sports Medicine.** Princess Kaiulani Hotel, Waikiki, Honolulu, Hawaii. Mon-Fri. 18 hrs. $300. Contact: Ms Joy Lewis, Box CEW-CCECS, 2530 Dole St, Honolulu, HI 96822. (808) 948-8244.

July 27-31—**Sports Medicine Update—1987.** UCSD at San Diego Princess Hotel, Vacation Village. Mon-Fri. 29.5 hrs. $325. Contact: UCSD.

SURGERY

March 18-20—**Preoperative Evaluation of the Surgical Patient.** UCSF at Holiday Inn Union Square, San Francisco. Wed-Fri. 16 hrs. $325. Contact: UCSF.

March 30-April 10—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Mon-Fri. 100 hrs. $1,750. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

April 11-18—**Surgery.** University of Washington at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: University of Washington School of Medicine, Div of CME, Sc-50, Seattle, WA 98195. (206) 543-1050.

April 30-May 2—**American Back Society Spring Symposium.** Anaheim Hilton Hotel. Thurs-Sat. Contact: Aubrey A. Swartz, American Back Soc, 2647 E. 14th St, Ste 401, Oakland 94601. (415) 536-9929.

April 30-May 2—**Postgraduate Course in General Surgery.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

May 11-15—**The San Francisco Orthopaedic Review Course.** UCSF at San Francisco. Mon-Fri. 40 hrs. Contact: UCSF.

May 13—**Otolaryngology: ENT Infections.** LLU at LLU. Wed. 4 hrs. $60. Contact: LLU.

(Continued on Page 306)

(Continued from Page 305)

May 14-16—**Symposium on the Temporomandibular Joint.** UCSF at Hyatt Regency, Monterey. Thurs-Sat. Contact: UCSF.

June 4-5—**16th Annual Neurosurgical Postgraduate Course.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

June 5-6—**6th Annual Southwestern Regional Cutaneous Flap Workshop.** UCLA at UCLA. Fri-Sat. 11 hrs. Contact: UCLA.

June 14-20—**Temporal Bone Surgical Dissection—1987.** House Ear Institute, Los Angeles. Sun-Sat. 62 hrs. $950. Contact: Antonio De la Cruz, MD, House Ear Institute, 256 S Lake St, Los Angeles 90057. (213) 483-4431.

OF INTEREST TO ALL PHYSICIANS

March 16-20—**Epidemics, Pandemics, and Mass Hysteria: From Antiquity to AIDS.** Kauai Foundation for Continuing Education at Poipu Beach, Kauai, Hawaii. Mon-Fri. 19 hrs. Contact: David J. Elpern, MD, Kauai Foundation for Continuing Education, PO Box 3650, Lihue, HI 96766. (808) 245-1507.

March 16-27—**Sexually Transmitted Disease (STD) Clinician Trng Course—Comprehensive.** Long Beach Health Dept and UCI at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, Long Beach 90806. (213) 427-7421.

March 19-27—**Specialty Series in Primary Care: Cardiology, Infectious Diseases and Endocrinology.** UCSD at Palm Springs Spa Hotel. Thurs-Fri. Contact: UCSD.

March 26-28—**CPR Update/ACLS Recertification.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Sat. 21.5 hrs. $350. Contact: UCSF.

March 28—**Management of the Menopause: Osteoporosis and Estrogen Replacement Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Dept of Academic Affairs, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 30-April 2—**Perspectives in Family Practice.** UCLA at King Kamehameah Hotel, Kona, Hawaii. Mon-Thurs. 20 hrs. $400. Contact: UCLA.

April 4-5—**Diabetes Update: 2nd Triennial Conference.** Cypress Foundation at Hyatt Regency Monterey. Sat-Sun. 10 hrs. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

April 6-10—**Drug Therapy.** University of Washington at Kona Surf Resort, Hawaii. Mon-Fri. Contact: Univ of Washington, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 13-17—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept and UCI at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

April 20-23—**Selected Topics in Dermatology and Pulmonary Intensive Care.** LLU at LLU. Mon-Thurs. 16 hrs. $400. Contact: LLU.

April 23-25—**37th Annual Regional Postgraduate Institute for San Joaquin Valley Counties.** CMA and Fresno-Madera Medical Society at Curry Village Pavilion, Yosemite. Thurs-Sat. 12 hrs. $150-200. Contact: Janice Rigney, CMA.

April 25-26—**Transurethral Ureteroscopy: A Seminar and Workshop.** UCSD at La Jolla Marriott Hotel, La Jolla. Sat-Sun. 13.5 hrs. $275-400. Contact: UCSD.

May 11-12—**6th Annual Physical Abuse: The Traumatized Child and Family.** UCD at Sacramento Inn. Mon-Tues. 11 hrs. $100. Contact: UCD.

May 11-13—**Arthritis Update '87.** Sharp Memorial Hospital, San Diego and UCSD at Hyatt Islandia Hotel, San Diego. Mon-Wed. Contact: Mary Belich, Sharp Memorial Hospital, 7901 Frost St, San Diego 92123-2788. (619) 541-3400.

June 8-13—**UCI Family Practice Refresher Course.** UCI at Newport Beach. Mon-Sat. Contact: UCI.

June 15-19—**Sexually Transmitted Disease (STD) Clinician Training Course—Advanced.** Long Beach Health Dept and UCI at Long Beach. Mon-Fri. Contact: Anne-Renee Heningberg, Long Beach STD Trng Ctr, PO Box 6157, Long Beach 90806. (213) 427-7421.

June 28-29—**9th Annual Poison Control Center: Management of Drug Overdose and Poisoning.** UCSF at San Francisco. Sun-Mon. 14 hrs. $235. Contact: UCSF.

July 6-9—**Family Practice Board Review.** UCSF at UCSF. Mon-Thurs. 25 hrs. Contact: UCSF.

August 16-26—**30th Anniversary Postgraduate Refresher Course—Program I.** USC at Sheraton Waikiki Hotel, Honolulu and the Marriott Hotel, Maui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1919, outside California, (800) 421-6729.

August 23-September 2—**30th Anniversary Postgraduate Refresher Course—Program II.** USC at Marriott Hotel, Maui and the Waiohai Hotel, Kaui, Hawaii. Sun-Wed. 37 hrs. $535-585. Contact: USC, in California, (800) 321-1929, outside California, (800) 421-6729.

IDAHO

March 14-21—**How to Make Fitness and Health Promotion Work in Your Practice.** Sun Valley. One week. 24 hrs. Sponsors: University of Arizona, Department of Family and Community Medicine, and Epic Medical Expeditions. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley 83353. (208) 788-4995.

March 19-20—**Idaho Thoracic Society Annual Symposium.** Anderson Center, Boise. Thurs-Fri. 8 hrs. $20, members; $40, nonmembers. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

July 27-August 2—**Idaho Medical Association Annual Meeting.** Coeur d'Alene. One week. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

MONTANA

April 3-4—**Montana Medical Association Interim Meeting.** Colonial Inn, Helena. Fri-Sat. Contact: MMA, 2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000.

June 18-20—**Montana Academy of Family Physicians—Annual Meeting.** Fairmont Hot Springs, Anaconda. 17 hrs. Contact: John Patterson, MD, 7 E Beall, Bozeman 59715. (406) 587-5123.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 14—**New Mexico Pediatric Society Wylder Lecture—Pediatric Neurology.** Albuquerque. Sat. Contact: NM Pediatric Society, (505) 758-8651.

March 14—**Perfecting Your Cardiac Physical Diagnosis Techniques: Lessons From a Master—A Symposium by W. Proctor Harvey, MD.** Albuquerque. Sat. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

(Continued on Page 310)

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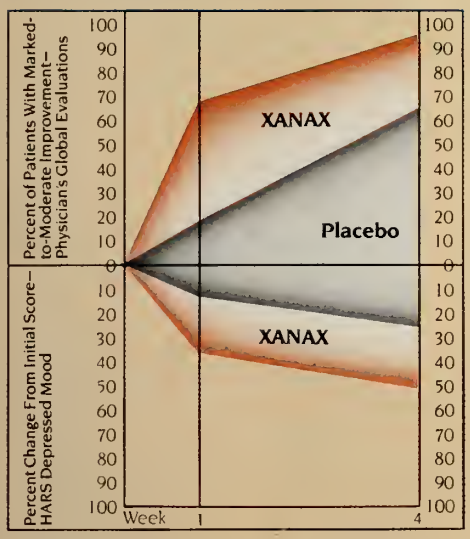

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than does placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items, including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- Effectively relieves the symptoms of anxiety
- Also relieves anxiety with associated depressed mood
- Well tolerated—side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions
- Does not cause cardiovascular toxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB: Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients *Curr Ther Res* 1984 35(1):100-112

Xanax® 0.25 mg Tablets

alprazolam Ⓘⓥ

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Please see adjacent page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

Upjohn THE UPJOHN COMPANY J-7382
Kalamazoo, Michigan 49001 USA February 1987

CONTINUING MEDICAL EDUCATION

(Continued from Page 306)

March 19-20—**Cultural Issues in Family Therapy.** Albuquerque. Thurs-Fri. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

April 9-11—**9th Annual Pediatric Cardiopulmonary Update.** Albuquerque. Thurs-Sat. AMFAC Hotel. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

April 24-25—**Practical Orthopaedics in the Primary Care Setting.** Albuquerque. Fri-Sat. Veterans Administration Medical Center. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

May 6-8—**New Mexico Medical Society—Annual Meeting.** Albuquerque. Wed-Fri. Clarion Four Seasons. Contact: NMMS, 303 San Mateo NE, #204, Albuquerque 87108. (505) 266-7868.

May 15-16—**Biological and Ethical Dimensions of Human Transplantation.** Albuquerque. Fri-Sat. Contact: Office of Medical Education, Presbyterian Hospital, PO Box 26666, Albuquerque 87125. (505) 841-1225.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

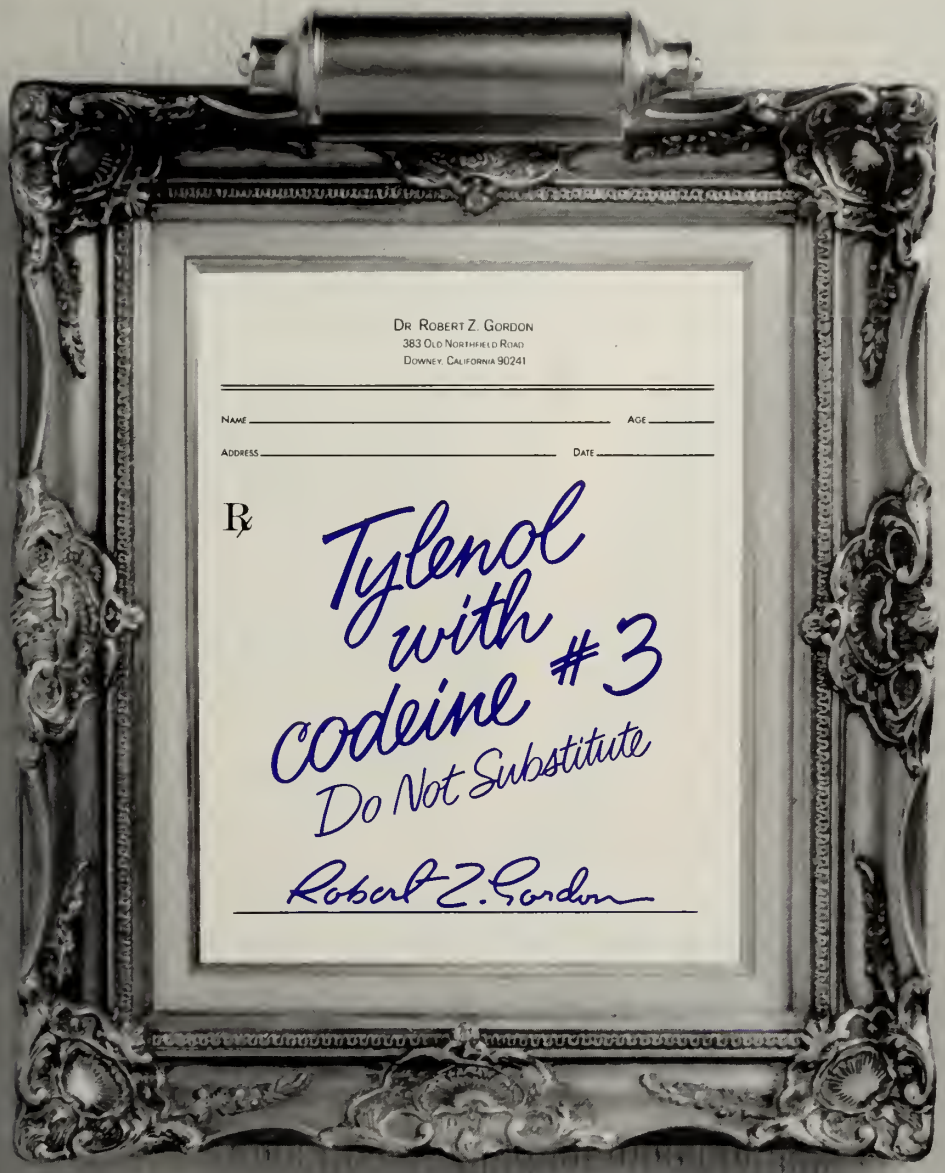
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

(Continued on Page 385)



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Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperg cemia and glycosoria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should develop, corrective measures should be taken such as potassiu supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevate serum potassium. Chloride deficit may occur as well as dilution hyponatremia. Concurrent use with chlorpropamide may increas the risk of severe hyponatremia. Serum PBI levels may decreas without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithiu toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, he ache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postu hypotension (may be aggravated by alcohol, barbiturates, or nar ics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vert have occurred with thiazides alone. Triamterene has been found renal stones in association with other usual calculus componen Rare incidents of acute interstitial nephritis have been reported Impotence has been reported in a few patients on 'Dyazide', altho a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsul in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Guest Editorial

Robert G. Wilson, M.D.

ARIZONA MEDICINE

JOURNAL OF ARIZONA MEDICAL ASSOCIATION

MARCH 1987, VOL. XLIV, NO. 3

The PRO: We *Must* Be Involved!

Although I practiced medicine for the past twenty years, only the last three have been in Arizona. And, I have never met Dr. Block. However, I was active in the PSRO effort in a neighboring state for several years prior to my move to Arizona; and I must quickly come to Dr. Block's defense when he correctly states that it is most important for physicians to stay totally involved in the review process.

There is little question that those who pay the bills want accountability; the federal government, the states and all other third parties. They deserve it. Over a billion dollars a day for health care is a large sum, and the public wants to be assured that it is getting full (and needed) service for this expenditure.

Up to this time, PSROs and now PROs have been mainly looking for "bad apples," or "aberrations," as Dr. Block calls them. But, these have been relatively few in number in all PROs. And, they don't really cost much money. The future push, however, may be to move, not just the "tail," but the "center" of the bell shaped curve of various medical activities to more necessary or more cost-effective behavior. This is how large savings may be achieved. Differences in philosophy may need to give way in the end to simply what is the most cost-effective means to a quality outcome.

Dr. Block is also correct in saying that outpatient care, particularly surgery, will now need to be monitored. Honest physicians should neither be afraid of nor offended by this prospect. Indeed, we should welcome such review as being helpful in the long run for our reputations as physicians and for the survival for our health care system. Giving in gracefully to a "look-see" does not mean giving up the way we do things, if the way we do things is what our patients wanted in the first place.

On the other side of the coin, PROs can best monitor quality if, by shifting certain bell shaped curves too much, it begins to cause patients to suffer. Certainly we have always needed a more structured way to measure quality. This may be the best we have at present.

Finally, with the ever rising tide of diffusion of new technologies, the expense of which is becoming unbearable even for the richest nation on earth, we desperately need a vehicle for their assessment. Some of these technologies may need to be promoted as cost effective or even as cost saving; some may need to be curtailed as being marginally effective; some may have to be "dropped" as being not worth the limited quality they provide to the very few. The PROs may turn out to be the best vehicle we have to carry out hands-on assessment and to transmit conclusions to the medical community, which can change the delivery of hi-tech care in more equitable and cost effective ways.

Many voices in our nation, from diverse quarters, are calling for a single system, national health insurance, as the only way to stop the ever rising cost of health care. We providers can no longer ignore our responsibility in doing all that we can to curtail this rise, and to demonstrate this effort to the public. The PROs are making their best attempt. It may be the physicians' last chance. I applaud the Arizona physicians who have taken it upon themselves to perform these useful review services. I believe that the silent majority of practicing physicians favors and does not fear their efforts. Should they fail to continue we may be assured that others, even less palatable to our xenophobes, will take over. ■

Robert G. Wilson, M.D.
Prescott, Arizona

Arizona Medicine is published monthly by the Arizona Medical Association, Inc. • 810 West Bethany Home Road • Phoenix, Arizona 85013 • (602) 246-8901.

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Marshall B. Block, M.D.

To Evolve or Not — That is Not the Question

As I was sitting in front of our home computer using the word processor software, trying to compose this editorial, the phone rang and I found myself again in conversation with Charles and Beatrice, my father and mother, who were calling long distance from Florida. "Do you know how many pills we take each day?" I knew this was a rhetorical question, so I just listened and didn't answer. "Thirty-two pills! Can't you send us a monthly package with our medications from the samples you get?" (I knew this one wasn't rhetorical). "Dad," I answered "why do you want me to send you the medicines? If it's the cost, I'll send you a check every month to cover their expense." He was silent for a moment before responding. "We don't want your money, we just don't want you to forget us!" His answer floored me. It was deja' vu! There I was, 12 years old, in summer camp, eagerly awaiting the "care package" filled with goodies from my parents. Now, I was fulfilling the paternal role, and they had become the children! Our roles had evolved with time without my even knowing it.

So, too, are all of our roles changing as medicine is heading into uncharted waters. While writing this editorial I took a call from the emergency room regarding an elderly patient with stomach cramps. The workup was all normal, but the emergency room physician told me she should be admitted as she "looked sick." Previously, I would have told him to "admit her." Now I responded by saing, "How can we justify the admission?" Although I'm not sure the change in orientation is all bad, I have altered my approach to the patient by events bearing no relation to her immediate problem. This subtle change has made me less of a patient advocate than I was before, and I didn't really realize it at the time.

Other changes, perhaps less extreme, are creeping into our daily activities as financial concerns begin to have a greater impact. Discussing the changes in Medicare reimbursement over breakfast at one of the local hospitals, one internist commented that when they reviewed their Medicare profile, they noted that they didn't perform many knee x-rays in their office, and perhaps this was an oversight. Another cardiologist noted that their profile for cardiac ultrasound was below the average and they could increase their fees to that level. Each in his own way was responding to external pressures, and was having their clinical skills influenced by these forces. I recently received a letter asking if I was interested in a lump sum payment to care for patients with endocrine problems for a local health maintenance organization. At first blush, the idea sounded pretty enticing, until I realized that my performance as a physician could conceivably be influenced by such an arrangement. Doing less and seeing more patients in a shorter period of time could jeopardize the care I administered to these patients. When thought of in that light, the advantages certainly did not outweigh what I saw as a major shortcoming of that kind of system.

We are all going to be faced with similar decisions and need to be cognizant of these evolving roles and guard against them. The question is not whether to evolve, but how to do it without changing our role as a patient advocate. We can't fall prey to the barons of merchandising, who want medicine to be a commodity rather than a calling. ■

Marshall B. Block, M.D. Editor

Peace of Mind

Life is rather like a campfire. Over the embers one might finally toast a few morsels of contemplation.

1. Most important of all is facility in expressing one's self. Virtually every observation we make is abstracted and coded into silent or audible speech and thence into memory. The vocabulary of man is infinitely richer than the gestures and grunts and cries of the animal. The loneliest and most vulnerable people in the world are those who cannot communicate their thoughts and feelings or tell of their experiences. And groping in unrelieved confusion is the individual who does not even have words with which to understand himself.

2. Equally important but sorely neglected is the faculty or function of imagination. The stepping stones of learning are the similes and metaphors which issue from the imagination. With their concrete help we progress from the known toward the unknown, from the familiar into the mists. Given anything new and strange we first ask ourselves, "what does this remind us of?" Hard as a rock, ice-cold, burdened with grief, dogged pursuit — even so esoteric an idea as the double helix of reproduction was conceived in fantasy.

Without imagination one is impervious to compassion. The viciousness of some psychopaths is because they cannot imagine the unspeakable sufferings which they are willing to inflict. When we fail to cultivate fantasy we end up with shrunken minds and hearts of gristle. Like cattle, we never raise our heads to look at the constellations. And, of course, we remain indifferent to any and all of the arts.

3. Perfectionism has been devaluated in modern religion and psychology. Yet the traits and practises of the perfectionist — his punctuality, for example, result in a certain predictability, and this is finally reassuring to those around him. It would seem easier to have to answer to one's own demanding conscience than to provoke and endlessly recoil in anticipation of the ridicule and annoyance of others. If, in fact, you are what you do (doctor, teacher, policeman, parent) then you must do it with scrupulous expertise or your self-esteem will always go begging.

4. Alongside perfectionism, and not without intelligent and circumstantial flexibility, one might foster a bit of asceticism. The biblical injunction, "Keep Holy the Sabbath," merits a pause for explication. Early in life one ought to make a resolution to abstain from any potential vice at least on that one day a week; not smoke or drink, for example, or overeat or pick at one's face or gripe. Anyone who can do without this or that substance for twenty-four hours or refrain from indulging whatever bad habit will feel that he is in control of himself, and this is essential to peace of mind.

With regard to any addiction one should be reminded of the enormous chasm between wishing and willing. (Lat., voleitas vs. voluntas). For years I wished to quit smoking but I was never really willing. Not mindful of the distinction, I blamed a lack of willpower. This proved to be a mistake and very self-defeating.

4b. Wishing and wanting are largely conscious and therefore fairly rational. Willing is influenced more by wordless pressures from the depths of the mind, and these pressures do include endocrine and hereditary vectors.
Hence, willingness to give up a harmful vice is by no means as simple as it sounds. A person may be almost unbearably bored and unhappy and dreading an empty future. Weighed down by duty and not disposed to self-pity, he may cling to his drinking or smoking, for example, as at least something to look forward to. Lacking insight he may be vaguely reluctant to take better care of himself lest renewed energy might push him clear out of bounds — into divorce or adultery or suicide or some other rebellion against stifling responsibilities.

5. Worth in any endeavor or accomplishment begs for simplicity. The efficiency expert as well as the artist will always strive to get rid of the dross and the glut. Ornamentation is usually primitive or childish. Things that serve no purpose do not belong in a factory or in a formula. The key term is refinement, as in the processing of oil or the extraction of precious metals or in one's deportment and dress.

(Continued on page 6)

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(Continued from page 4)

Anything that serves no purpose has no soul, for soul is simply the reason for the organizing of the parts of a functioning unit. The soul of an automobile is its usefulness for transportation. The soul of a work of art is its ability to convey an ineffable message and stir aesthetic appreciation.

The significance of simplicity applies especially to the person. To be an individual means literally not to be divided. Wherever a person seems too complicated he is probably neurotic.

5b. An immature person may be totally enmeshed in one or another of his various relationships — spouse, wage earner, church member, etc. If he has no separate identity of his own he will become fanatic, losing perspective and foregoing all other interests. He will be narrow-minded, self-important, humorless, defensive, pathologically jealous.

Relationships by definition are reciprocal; husband-wife, employer-employee, salesman-customer, lawyer-client. A person in any relationship can be disappointed or, worse, can be a disappointment. The derivative insecurity and ambivalence cannot be completely avoided. Hence any relationship is somewhat complicated, being sustained by small self-deceptions and some pretenses and impersonations.

The mature individual's traits and relationships will have become integrated into one whole and harmonious personality. He will seldom have to adopt superficial roles, impressing himself delusionally or beguiling others. Inevitable tribulations in any one of his relationships will not jerk him back and forth, taking away his dignity or driving him to despair.

A paradoxical note had better be acknowledged. We feel that we never really know certain of our friends. They are the ones who have indivisible personalities, independent of any of their relationships. There is no inherent dignity without a tinge of loneliness.

6. Vices are for the most part solitary. Against unhealthy eccentricity or repeated and serious errors in judgement, the most reliable protection is friendship. With surreptitious boozing or clandestine affairs one might deceive one's spouse (don't kid yourself!). But one had rather die than lose one's friends in disgrace. In this respect a very desirable recreation is any non-adversarial sport, any in which the competition is primarily with one's self and not aggressively toward one's companions. A good example is golf, with its joshing cameraderie.

7. A sense of humor can be a delightful display of quick-wittedness. Incessant joking, however, soon becomes an irritant, as does habitual drollness. Humor ought to be used as sparingly as salt and pepper. One should also bite one's clever tongue before joking at another person's expense. Pleasant teasing quickly sours into sarcasm, which is always offensive. Contrariwise, a chap constantly turned his derisive humor onto himself, belittling his own competencies. Unfortunately, he succeeded in convincing us that he was a dolt.

8. To a surprisingly important degree one's welcome in the world is assured by good manners. Only the stupid seem satisfied with their vulgarities and ignorance, dooming themselves to perpetual meanness and boredom. The humble fatalist, on the other hand, supposes that good breeding needs to have been inherited. Not really. Not blessed with exposure to finishing school, a man as well as a maiden can gain familiarity with the suggestions in any standard and sensible book of etiquette. A very ordinary acquaintance rode out to considerable prestige and affluence on little more than a well-groomed horse of courtliness. Good manners are horizontal girders in the scaffolding of dignity.

8b. The vertical beams are the virtues. In days gone by most virtues seemed negative — Thou shalt not. For the only earthly reward of virtue was avoidance of the consequences of vice. Take chastity, for example. Contraceptives, legal abortions, antibiotics, divorce, social indifference — all have conspired to mitigate the penalties of promiscuity. Honesty was surely the best policy when the punishment for theft meant getting your hand cut off! In our migrant society even ostracism is no longer a harsh punishment, nor is its risk an effective deterrent. What seems to be a breakdown in morality is really a breakdown in the consequences of immorality.

Alcoholism, by the way, is *not* a disease; it is one of vices which can lead to disease, and so with gluttony and other addictions and repugnant compulsions. Psychiatry has been criticized as relatively ineffectual in the field of alcoholism. Well, we can take responsibility for the treatment of a sick individual but the antecedent and culpable vice must still be the concern of the moralist — the parent, the teacher, the clergyman, the law.

So how come the sermon-like aspects of this essay? And written by a doctor? The reciprocating proverb, Mens sana in corpore sano, is never-the-less true. In the last analysis, virtue almost becomes synonymous with peace of mind. And peace of mind certainly prevents more illness than does anything in our armamentarium. ■

William B. McGrath, M.D.

AMA Admonishes ABC TV

The American Medical Association has taken a national television network to task for its lack of objectivity in presenting a Saturday, December 27 program that sensationalized the complex professional liability problem.

The program was an *ABC Close Up* presentation entitled "Diagnosis: Malpractice." Although the holiday season program had low viewership, many physicians have expressed concern to the AMA about the telecast's lack of balance and shallowness.

In a letter to Richard Richter, senior producer for *ABC News Close Up,* James S. Todd, M.D., AMA's Senior Deputy Vice President, pinpointed the show's major shortcomings and urged that *Close Up* develop a second program to place the professional liability crisis, its causes and its potential solutions in proper perspective for the public.

The full text of Dr. Todd's communication follows:

"Whatever the intent may have been, your recent *ABC Close Up* presentation entitled "Diagnosis: Malpractice" succeeded only in sensationalizing a very complex problem. The viewer was left with an inaccurate and frightening impression that each encounter with a physician is fraught with great danger. A great disservice is done by creating an atmosphere of distrust and fear among patients. The brief comment early in the program that the malpractice crisis is not the result of poor quality care was lost in the visual impact and emotional reporting of isolated incidents.

"Having contributed to your research data, we are at a loss to explain the absence of objectivity. We do not deny that negligence exists, but not to the degree indicated by the current level of litigation or the increasing level of awards made by juries.

"Physician discipline was given scant credit despite the joint actions of the Federation of State Medical Boards and the AMA to identify and eliminate errant physicians. Congressman Wyden was given great credit, ignoring the fact that organized medicine was instrumental in helping draft and pass his legislation.

"Insurance companies, highly regulated, were treated shabbily, especially by Robert Hunter, who repeatedly confuses insurance issues and is a spokesperson for the trial bar. You and he both have neglected to study physician owned, nonprofit monoline insurance companies that clearly have suffered intolerable losses in a judicial system where sixty percent of cases filed are without merit; fifty percent of dollars awarded go to five percent of the cases; and sixty percent of premium dollars are consumed by the system and never reach injured patients or physicians in the current system.

"We would have preferred that your program give some mention to the federal and state efforts to bring about changes in the tort system that preserve patients' rights while at the same time protecting hospitals and physicians against unwarranted litigation and excessive economic penalties. The cost of insurance under the current system is causing many physicians to curtail or leave their practices. One result is that some medical care, particularly in obstetrics, may be in short supply.

"Medical care is an inexact science. Under the best of circumstances, unfortunate results occur. Our current system fails adequately to distinguish between unfulfilled expectations and negligence. Your program missed the opportunity to educate health care consumers on what they can do to protect themselves from substandard care, and how the current level of litigation is diminishing the availability of needed care, inflating the cost of health care and stifling innovative technology.

"Given the huge number of patient-physician encounters every day, the medical profession can be proud of its accomplishments. At the same time the medical care system has some shortcomings that physicians and their professional organizations are working hard to correct. We would urge you to schedule a second broadcast to complete the liability picture, and we would be pleased to contribute to the content of a second program."

Unorthodox Prescription Formatting by Physicians

By Llyn A. Lloyd, Executive Secretary
Arizona State Board of Pharmacy

(Author's note: I am grateful for this opportunity to communicate an interprofessional concern with our health care colleagues in medicine and surgery. Contemporary concerns facing all professionals today transcend the age-old, and still primary, one of care to the patient, including tort reform, scope of practice, innovative practice sites, institutional players in the traditional individual practitioner profession.

The need is clear: communication with and between health care providers is crucial to the professional as well as to the patient. With this, I come bearing the concern of the Board of Pharmacy relevant to pharmacist confusion initiated by unorthodox prescription formatting. I invite your comments and questions.)

Confusion may exist among practitioners relevant to generic vs. brand name prescription writing and dispensing as well as prescriptions for controlled substances.

To illustate specific areas of concern, the following examples are submitted:

Example #1:
Theo Dur 300 mg
#30
Sig: 300mg q 12 h
Practitioner signs Rx on "Substitution Permissible" line.

Comment:
By state regulation, sustained released products are **not** substitutable. The pharmacist who is asked by the patient to dispense a generic product when the brand is prescribed is left with the options: (1) To contact the prescriber to request permission to dispense the generic product, rewrite the prescription as a telephone order, "void" the original prescription, and fill the replacement; (2) fill the prescription as written, using the brand name product; (3) illegally fill the prescription using a generic product and indicate that on the prescription; or (4) refuse to fill the prescription.

Suggestion:
When prescribing sustained release products with the intent that the pharmacist should dispense a generic product, the physician should write the order generically. The pharmacist is then authorized to select the actual product as long as it is FDA approved and distributed by a firm listed with the Board of Pharmacy as an approved manufacturer/distributor.

Example #2:
Dyazide
#30
Sig: i d AM
Practitioner signs on "Substitution Permissible" line.

Comment:
This is a relatively cut-and-dried case, since "Dyazide" is a single source drug. There is no generic equivalent; therefore, no substitution can occur.

Suggestion:
Practitioners could help avoid patient confusion by signing single source drug prescriptions on the "Dispense as Written" line.

Example #3:
This case involves an "emergency telephone order" for a C-II drug and does not lend itself to illustration by example. Presume Dr. Doe wishes to order tablets of Demerol 50mg for patient Mr. Public, whom Dr. Doe has just seen at Mr. Public's home. Dr. Doe telephones the pharmacist and orders 50mg Demerol p.o. q 4-6 h prn pain. Anticipating that Mr. Public could require medication for at least ten days, Dr. Doe orders 50 tablets. The pharmacist advises Dr. Doe that the law (in this case federal regulations) limits the quantity of C-II drugs ordered by telephone to a 72-hour supply, which in this case would be 18 tablets. Additional tablets must be ordered by written prescription.

Federal regulation further requires the practitioner to supply the written order to the pharmacist within 72 hours. Strictly applied, the pharmacist who does not receive the written prescription within 72 hours is required to notify the local office of the U.S. Drug Enforcement Agency.

Suggestion:
By knowing and respecting the state and federal requirements for controlled substance prescription writing, all parties will incur fewer delays, inconveniences and possible compliance violations which can create additional problems.

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Ambulatory Medical Education: New Initiatives, Part II

In a previous editorial we detailed the history of the change in emphasis in medical education from the inpatient to the ambulatory setting. In this segment we detail what is occurring at the University of Arizona College of Medicine.

The faculty-elected Curriculum Committee of the College is examining the issue of declining lengths-of-stay for hospitalized patients and the impact on education of our students. They are undertaking a thorough analysis of the curricular objectives of each clinical department in relation to the settings in which those objectives are currently being met. We anticipate that the outcome of this review will be the development of specific recommendations for alteration in specific clerkships, as well as an overall plan for ensuring adequate ambulatory education for all students.

Since the College was established on the premise that most clinical education would occur in hospitals, we anticipate that significant changes will be required should the Curriculum Committee's recommendations support increased ambulatory education.

As stated previously, movement of students from traditional inpatient settings to ambulatory settings requires shifting of faculty and support personnel, as well as reapportionment of supplies, equipment and other resources necessary to support students in the new sites. A small group of faculty and administrators have been asked to determine the resources necessary for this greater emphasis on ambulatory education. The scope of this ad hoc task force includes delineation of the costs required to sustain this important shift in educational effort, both in terms of personnel time and dollars.

Considerable ambulatory experience already occurs in certain courses and disciplines. In the interdepartmental course, Preparation for Clinical Medicine, students regularly attend patient encounters in preceptorships with physician members of our faculty in their offices throughout the community. Family Medicine is taught mostly by patient contacts in ambulatory clinics or physician-/preceptor offices. One-half of the required pediatric clerkship is devoted to experience in the clinic. Variable amounts of time are spent in other discipline clerkships in ambulatory settings. From patient-log records of encounters by our students we know that 52% of more than 3000 encounters reported by students are ambulatory; ranging from 99% in Family Medicine, through 62% in Obstetrics and 51% in Pediatrics, to 17-27% in General Surgery, Psychiatry, Specialty Surgery and Neurology. Internal Medicine has the least amount of ambulatory contact (1%), consistent with their traditional educational philosophy of focusing medical student education with hospitalized patients.

With such a seemingly large amount of existing ambulatory education, one may wonder why there is concern. As stated in our first editorial, even those disciplines with established large volumes of ambulatory activity, and definitely those which have been primarily inpatient and consultative in nature, are experiencing the effect of the decline in length-of-stay and the change in style of practice. This increasingly places more care, and especially more complex care, in the clinic and office. Thus, the educational focus must broadly change, and some increase in ambulatory education must occur in those disciplines which traditionally have taught almost exclusively in inpatient sites. For example, general surgery has begun to shift its student educational emphasis to the outpatient arena in the recognition that students needed greater experience with surgical judgment and evaluation pre-operatively, and with post-operative care. The shift to ambulatory and one-day surgery was increasing, resulting in students first seeing the patient anesthetized and about to undergo a surgical procedure. The shift to include outpatient educational opportunities should improve attainment of surgical learning objectives by allowing students to observe and participate in pre-surgical judgment, and to encounter patients for whom the decision is *not* to perform a surgical procedure.

The practices of patient care are changing. The educational response is also moving apace. The changes are expected to enhance learning and better prepare our students for the practice of medicine today, and as encountered in residencies and in active practice careers in the future. ■

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Physicians in the News

John T. Clymer, M.D.

John T. Clymer, M.D., a Tucson psychiatrist took office as the 1987 Pima County Medical Society president at the society's dinner meeting January 13, at its headquarters, 5199 East Farness. He succeeded Paul D. Dempsey, M.D., D.M.D.

Clymer had asked Patricia Nolan, M.D., director of the Pima County Health Department, to speak at the meeting. "Society members have expressed a real concern about public health problems in this community and their desire to do something about them," he said. "We're looking to Dr. Nolan to outline major problems and suggest possible courses of action for PCMS."

Other new officers of the society are James J. Corrigan Jr., M.D., professor of pediatrics at the University of Arizona College of Medicine, who has been named president-elect; James H. Reifschneider, M.D., an internist at the Thomas-Davis Medical Center, vice president; and Janis K. Johnson, M.D., an anesthesiologist, secretary-treasurer.

Clymer, 61, grew up in Michigan. His undergraduate studies at Northwestern University were interrupted by three years of Navy service in World War II. He was graduated from the University of Michigan Medical School in 1952, took his internship at Henry Ford Hospital in Detroit, and then came to Arizona in 1953 for a residency in general practice at Maricopa County Hospital in Phoenix. He was a family doctor in Phoenix until 1965, when he returned to Michigan to take a three-year residency in psychiatry at Ypsilanti State Hospital. In 1968 he opened his solo practice in psychiatry in Tucson.

Clymer is a past president of the Arizona Medical Association (1980-81) and a past president of the Tucson Psychiatric Society. He has been active in state and local committees on physicians' health and is a member of the State Bar of Arizona's Committee on Mental Health.

His hobby is bicycling and he takes it seriously. Clymer has participated in two "Almost Across Arizona" rides, El Tour de Tucson, the Dalmac tour in Michigan (which runs from Lansing to the Straits of Mackinac), and even bicycles to Phoenix for Arizona Medical Association meetings. He's a strong advocate of cycling safety and is proud of a public service announcement he made for the medical society which stresses the importance of helmets for bicyclists.

His biggest concern this year is helping physicians adjust to the changing patterns of medical practice sweeping over America. ■

Donald L. Damstra, M.D.

Donald L. Damstra, M.D., Phoenix, Director of the Arizona Medical Association's chemical dependency program for impaired physicians, was at the top of the first group of physicians in Arizona to pass the certification examination of the American Medical Society on Alcoholism and Other Drug Dependencies.

This is the first year the innovative examination has been given on a national

basis in an effort to identify physicians' expertise in the rapidly growing field of treatment for alcoholism and other drug dependencies. Out of some 2500 members of the American Medical Society on Alcoholism and Other Drug Dependencies, only 730 have taken the exam.

"The field of alcohol and drug dependence treatment is growing rapidly in response to increased awareness of what's considered by many to be a major national medical problem," said Max Schneider, M.D., president of AMSAODD. "Certification is a way to identify those physicians who by testing have shown a mastery of the body of knowledge that has now been amassed in this field."

The five-hour examination covers alcohol and other drugs of abuse, with questions equally divided between clinical issues and basic science. Recertification will be required after seven years.

Dr. Damstra has been director of the Arizona Medical Association's dependency program since January, 1986. In that role, he has been responsible for supervision of efforts to verify reports of physician impairment, identification of the seriousness of reported problems, intervention when appropriate, development of treatment plans, and monitoring aftercare treatment.

Dr. Damstra will be among those whose certification in chemical dependence will be presented during AMSAODD's annual meeting and scientific conference in Cleveland in April.

The next national AMSAODD certification examination is scheduled for December 5, 1987. Applications must be received by March 15. Additional information about the certification program can be obtained from AMSAODD, 12 West 21st Street, New York, N.Y. 10010, or by calling AMSAODD headquarters, (212) 206-6770. ■

Saul N. Schreiber, M.D., will present a paper at the International Arthroscopy Association-Triennial Scientific Meeting April 2-4 in Sydney, Australia.

Dr. Schreiber, a Phoenix orthopedic surgeon, will speak on the topic "Lateral Retinacular Release: Using a Modified Superomedial Portal, Electrosurgery and Post-op Positioning in Flexion.

The procedure uses an interchangeable Cannula System such as the one Dr. Schreiber designed which is now manufactured by Wolf Medical Instruments. The technique facilitates patellar evaluation and performance of lateral release under direct vision, minimizing complications and allowing early motion. ■

Alan L. Gordon, M.D., Phoenix, has been elected to the American Board of Internal Medicine. ■

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Pathologists and other medical professionals from universities, medical centers, industry and government are invited to submit scientific abstracts for presentation as papers (residents only) or in a poster format at the forum. Thirty of the accepted abstracts will be published in the *American Journal of Clinical Pathology*. The deadline for submission is May 1, 1987.

The two residents presenting the best papers will win cash awards of $500 as part of the Pathology Resident Awards Competition. On the basis of the abstracts, ten papers will be selected for presentation, five each in anatomic and clinical pathology. The final award winners will be selected on the basis of both content and presentation of the papers. Residents must be currently enrolled in a pathology program to participate.

For complete information and an abstract reproduction form, contact: **Manager for Scientific Assembly, American Society of Clinical Pathologists, 2100 West Harrison Street, Chicago, Illinois 60612-3798.** ■

Screen for Teen Drug Abuse Risk

Screening for drug and alcohol use and risk factors is not routine practice in primary care pediatrics. But a study in January's *American Journal of Diseases of Children* suggests a simple questionnaire completed in a doctor's office can gauge substance abuse risks in adolescents. Michael Klitzner, Ph.D, of the Pacific Institute for Research and Evaluation, Bethesda, Maryland, and colleagues administered the 42-item questionnaire to two groups: 97 youths from a drug abuse treatment program and 206 youngsters from a private pediatric practice. The questionnaire, which asked about various behaviors and the youths' relationship with their parents, was able to discriminate between the two samples, the study finds. It also appeared capable of discriminating alcohol and drug abuse within the samples, they say. ■

Dermatologists Disagree on Minoxidil

Enthusiasm for minoxidil, the experimental topical drug for baldness, varies widely among dermatologists, a study in the January *Archives of Dermatology* reports. A small number of dermatologists frequently use the drug but "the overwhelming proportion of dermatologists prescribe it to fewer than one new patient per week," says the study by Robert S. Stern, M.D., of the Beth Israel Hospital and Harvard Medical School, Boston. Stern surveyed a random sample of members of the American Academy of Dermatology and found that although more than 70 percent responding had prescribed minoxidil for hair loss, less than 10 percent of this group accounted for more than half the reported prescriptions. Stern says the low general prescription rate "may reflect either skepticism about the clinical effectiveness of the drug or concern about its cost," the two spontaneous comments cited most in the survey. ■

Who Has Nightmares?

Frequent nightmare sufferers have particular personality and psychological traits that differ from those of other dreamers, says a study in January's *Archives of General Psychiatry*. Ernest Hartmann, M.D., of the Tufts University School of Medicine, Boston, and colleagues, studied 12 lifelong nightmare sufferers, 12 vivid dreamers who had no nightmares and 12 people who had neither nightmares nor vivid dreams. The nightmare sufferers consistently scored higher than the others on the "psychotic" side of the Minnesota Multiphasic Personality Inventory profile and had more close relatives with nightmares and psychological problems. Interviews showed the nightmare sufferers to be sensitive and "open" people, some of whom had features of "schizophrenic spectrum disorders," but who also had artistic and creative tendencies and interests. The study concludes that nightmare sufferers don't have powerful hostilities or an unusual number of fears, but that the fears and feelings common to most people "get through" to their dreams "more than they do in most of us." ■

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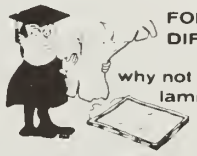

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Rapid Fluid Replacement for Severe Hypovolemia—Human Subject Trials

KENNETH V. ISERSON, MD, *and* ALAN K. REETER, MSEE, CCE, *Tucson*

Successful resuscitation of a hypovolemic patient often requires rapid intravenous administration of massive amounts of fluid. A new fluid system, incorporating a 14 French percutaneous catheter and a fluid reservoir, was recently developed and successfully tested in animals. We report the system's use in five patients with severe hypovolemia following trauma. In two cases, the experimental high-flow system successfully resuscitated the patients, allowing them to be transferred for further care. Problems associated with the use of the system included complications with central line placement and physician acceptance. This system offers an alternative that delivers these fluids in one line at rates above most current commercial systems.

(Iserson KV, Reeter AK: Rapid fluid replacement for severe hypovolemia—Human subject trials. West J Med 1987 Mar; 146:313-315)

Numerous authors describe the need to promptly initiate fluid resuscitation in patients with severe hypovolemia.[1-7] This need has prompted much experimentation with various catheter-tubing combinations to develop a system capable of delivering fluids intravenously more easily and rapidly.[1-10]

A new method was recently introduced for rapid fluid replacement, capable of delivering two liters (or more) of fluid per minute in animals.[5,6] This system consists of a specially designed 14 French catheter and fluid reservoir device. The reservoir allows intravenous (IV) delivery of fluid through one large-bore, central catheter. The rates obtained from this are enough to obviate the need for the many peripheral and central IV lines normally associated with hypovolemic resuscitation. In the tests in animals, vein wall damage and catheter insertion difficulties, expected from the large catheter, were similar to those found with current catheters. Based on the results of these trials, authorization was obtained to use the system on a specific patient population. The goal of this study was to evaluate the feasibility of using this IV fluid delivery system in patients with hypovolemia following trauma.

Patients, Materials and Methods

Guidelines for implementing the system in the emergency department were established by the University of Arizona Human Subjects Committee. These guidelines included using the system only on moribund patients.

Potential participants were identified, when possible, in advance of arrival by communication from the paramedic unit at the scene of an accident. The decision to use the system was based on telemetry information or a patient's clinical state on admission. Operative intervention was never postponed or delayed to use the IV system.

Readers are referred to previous publications for a detailed description of the components of the high-fluid-flow system.[5,6] Briefly, five IV bags empty (by gravity or external pressure) into a fluid reservoir; the crystalloid-blood mixture is then infused into the patient by way of a specially designed 14 French (4.5 mm internal diameter), 17.1-cm long polyethylene catheter. The catheter is placed into a large central vein using the Seldinger technique (Figure 1). The rate, duration and amount of fluid therapy are guided by the response of vital signs and vital organ function in the individual patient. Provisions were made to exchange the 14 French catheter for a standard 8 French if the patient was transferred out of the emergency department for further care. Chest radiographs were taken in three patients to confirm the catheter position.

An autopsy was done on four out of the five patients in this study. This allowed the venous system and heart to be inspected for any damage caused by the catheter or rapid fluid flow. A correct catheter position was verified in all cases, including the two cases in which chest radiographs were not done.

Results

The rapid infusion system was used on five patients with severe trauma over a five-month period.

The population consisted of three patients with gunshot wounds and two with multiple trauma resulting from a motor-vehicle accident. Two patients were successfully stabilized using only the high-fluid-flow system. Patient 1, a motor-vehicle-accident victim, was unresponsive at the scene but had a palpable systolic blood pressure of 60 mm of mercury and pulse of 150 per minute when arriving in the emergency department. The 14 French catheter was easily and rapidly placed in the right subclavian vein, and the patient received five liters of crystalloid and two units (mean 299 ml per unit erythrocytes at this institution) of erythrocytes (22 liters per hour) before stabilizing. The 14 French catheter was ex-

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changed for an 8 French before transfer to the operating room. The vital signs on leaving the emergency department were blood pressure 100/60 mm of mercury and pulse of 85. The patient underwent exploratory laparotomy and was then transferred to the intensive care unit for monitoring. Despite a stable cardiovascular system, no improvement was noted in the level of consciousness. Brain death was determined on day 3 of hospital stay, with subsequent removal of the kidneys for transplantation. An autopsy showed no damage to the right subclavian vein resulting from the catheter placement.

The second case of successful stabilization occurred in a gunshot victim with wounds to the right chest and left arm. Vital signs were initially present at the scene of the trauma. During transport the patient's condition deteriorated and he went into cardiac arrest about three minutes before arrival. On arriving at the emergency department, the 14 French catheter was placed in the right internal jugular vein without difficulty, and the patient received eight liters of crystalloid and six units of erythrocytes (28.5 liters per hour) to restore the blood pressure and pulse. The 14 French catheter was exchanged for an 8 French to be used in the operating room. On leaving the emergency department, a blood pressure of 90/50 mm of mercury and spontaneous heart beats were recorded. An exploratory laparotomy showed massive abdominal injuries that could not be completely repaired. Despite surgical intervention, the patient was pronounced dead 3 hours and 40 minutes after admission. An autopsy showed no damage to the vein from catheter insertion.

The remaining three patients, despite aggressive resuscitation, died in the emergency department. The third patient presented in traumatic cardiac arrest following a motor-vehicle accident. Electrical activity was reestablished in the heart following placement of the 14 French catheter and infusion of 12.5 liters of crystalloid and 7 units of erythrocytes (41 liters per hour). Despite the adequate volume replacement, the patient remained in electromechanical dissociation and was subsequently pronounced dead. An autopsy showed no abnormal findings in the structure or integrity of the catheterized vein.

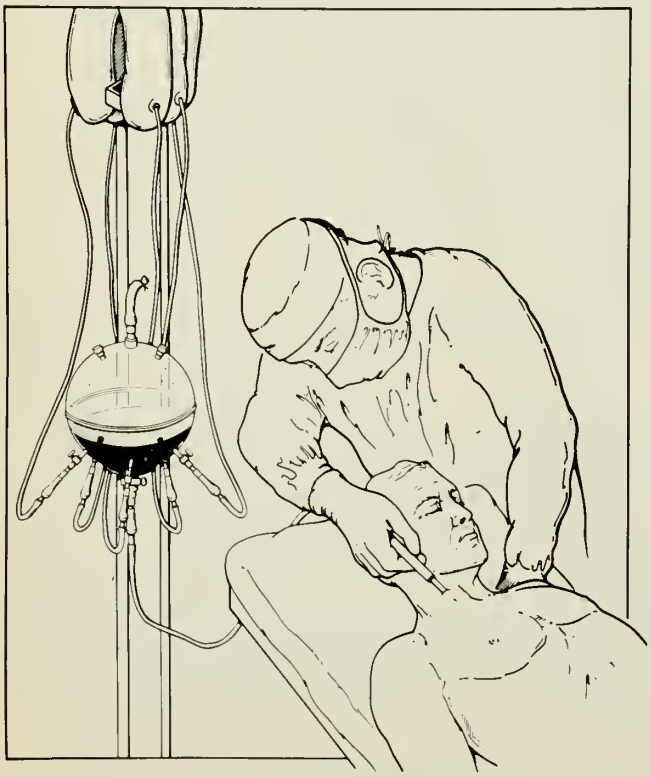

Figure 1.—Insertion technique and configuration of the high fluid flow system (from Iserson and Reeter[6]).

Patient 4 was a victim of a gunshot wound to the suprasternal notch. On admission to the emergency department, a 14 French catheter was placed in the right internal jugular vein and 8.6 liters of crystalloid and 3 units of erythrocytes (32 liters per hour) were infused. The patient's condition began deteriorating despite aggressive fluid resuscitation, resulting in a cardiac arrest. A left thoracotomy showed a flaccid, empty heart. When the thoracotomy was extended to the right side, a superior vena caval disruption with free fluid flow was found. Despite attempts to occlude the defect, resuscitation was unsuccessful and the patient died. An autopsy revealed that the vein disruption was the result of the bullet and not from catheter placement.

The fifth patient was a gunshot victim with a wound to the left side of the chest. No vital signs were obtainable on admission to the emergency department. Several difficulties were encountered when attempting to place the 14 French catheter. These included difficulty isolating the vein due to hypovolemia and subcutaneous air from a pneumothorax. The patient was extremely obese, which added to the difficulty. A thoracotomy showed a hole in the left atrium from the bullet. Despite attempts to close the defect, no evidence of cardiac activity was ever obtained. No autopsy report was available on this patient.

Overall, the clinicians more experienced in central line catheterization placed the catheter easier and faster. The range of times for catheter insertion was from 30 seconds to a maximum of 6 minutes, independent of location. No excessive bleeding was noted either in the short term or in the one long-term survivor.

The four available autopsy reports showed no damage to either the vein walls from the large catheter or to the heart from the fluid flow. Some minimal changes, normally observed with the presence of any intravascular catheter, were seen. No major problems were encountered when exchanging the 14 French catheter for an 8 French before transfer.

Discussion

The methods used to achieve rapid volume replacement in patients with severe hypovolemia are varied. Some of these include increasing fluid tubing size,[4,11] increasing external infusion pressure from 300 mm of mercury to 600 mm of mercury,[9] using the Bentley autotransfuser with colloids[3] and inserting IV tubing directly into a vein via a cutdown.[4] Despite the varying methods, all agree that the key to hypovolemic resuscitation is the speed with which fluids can be delivered in relation to their loss.[1-11]

To achieve adequate fluid delivery in patients with severe hypovolemia using traditional IV lines, two or more lines must be inserted. Customarily, the IV lines are placed in both upper and lower extremities. This positioning makes it difficult to closely monitor the flow rate and total volume of the IV fluid infusions. The single-line system described here reduces "clutter" around a patient and improves a physician's ability to carry out procedures and to assess a patient's condition.

In addition, implementing the single-line reservoir system improves the functioning of smaller trauma-care rooms. Decreasing the number of lines to be initiated decreases the

technical time required during a resuscitation process and allows valuable staff to be used in other areas. In facilities with limited staff resources, this could mean an improvement in resuscitation survival.

In studies in animals using this reservoir system, volumes of two liters per minute or more were easily achieved without untoward effects on the venous vasculature. This was confirmed in these human trials.

We recognize that the survival rate achieved in this study is not overwhelming. There appear to be three reasons for this: (1) The inclusion criteria mandated that the patients be in a near-terminal state before our attempting to use the system. This limited our ability to clearly identify the effect of the system on patients with a less obvious outcome. (2) The aggressiveness of the physicians who used the system affected the potential outcome. In at least one case, the system was not implemented for about 30 minutes after a patient's admission, decreasing its potential usefulness. (3) There was irreparable damage to vital organs, even when patients survived to the operating room or the intensive care unit.

This study, then, because of the nature of the cases, was not designed to measure survival. Rather, the feasibility of using this IV fluid infusion system was being evaluated in hypovolemic patients. We expected that this sytem would improve survival in patients for whom rapid loss of bodily fluids is the critical mortality factor.

Under certain conditions, placing a catheter in the central venous circulation might not aid in the resuscitation procedure or be at all practical. Chest injuries occurring high in the thorax limit or preclude the use of neck veins for catheter placement. Field initiation of the pneumatic antishock garment and abdominal injuries limit the feasibility of the groin vessels for catheterization. An alternative to this might be the use of a large-bore peripheral IV line. Recent evaluation of a 12-gauge catheter for peripheral placement proved it to be equivalent in flow to an 8 French catheter.[11] Used in combination with the reservoir system, an excellent flow rate could be achieved without the risks of a central vein catheterization.[12]

Even with this system, an additional IV line may be needed to administer medications. All of the patients in this trial arrived in the emergency department with a line initiated by paramedic personnel in the field. In those patients without this prehospital intervention, consideration must be given to the placement of a medication line.

The massive infusion of fluids in a hypovolemic patient brings with it the possibility of life-threatening hypothermia. Using warmed saline along with large transfusions of cold blood or blood products has been an effective method of temperature control.[3,13] This method was used in this trial. Continuous temperature monitoring was not done during the infusions, nor were any other warming modalities used. Rectal temperatures of those who survived to reach the operating room or intensive care unit averaged 36°C (96.8°F; range 35.5° to 37°C). No severe temperature-related problems occurred in any of these patients.

Overall, the system functioned as expected. The low survival rate can be attributed to the severe injuries and near-terminal condition of the patients in this study. The problems that were encountered during the placement of the 14 French catheter were similar to those of placing smaller catheters. Difficulty locating a vein in a hypovolemic patient is a common problem, but it might be exacerbated by the larger diameter of the catheter. The autopsy reports from four patients, however, confirmed the minimal injury caused by a 14 French catheter in an appropriately sized vein.

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Clinical Medicine

Preserving Renal Function in Surgical Patients

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Postoperative acute renal failure, especially associated with oliguria, carries a high rate of mortality and morbidity. This complication can frequently be avoided if physicians are knowledgeable about preventable or modifiable risk factors. Patients who have underlying renal disease, sepsis, volume depletion or other conditions associated with renal hypoperfusion, or who have severe liver disease, are at particular risk. Exposure to nephrotoxic agents and wide fluctuations of intravascular volume are key conditions that can usually be minimized. Managing patients with chronic advanced renal failure (creatinine clearance 10 to 25 ml per minute) requires close interaction between the internists, anesthesiologists and surgeons. Understanding associated metabolic and organ system disorders is necessary to prevent complications and preserve remaining renal function. Chronic renal failure should not be a contraindication to an elective or emergent surgical procedure.

(Whiteside-Yim C, Fitzgerald FT: Preserving renal function in surgical patients. West J Med 1987 Mar; 146:316-321)

Mortality in patients in whom acute oliguric renal failure develops postoperatively has remained greater than 50% over the past 30 years despite advances in supportive care,[1,2] due in part to the development of more complex surgical procedures and more frequent surgical treatment of high-risk patients. The underlying reason for an operation and the overall health of a patient also determine the outcome. Though dialysis has decreased mortality in patients with postoperative acute renal failure[3] and total parenteral nutrition appears to be of value in their support,[4] the statistics remain grim. Nonoliguric renal failure, usually resulting from nephrotoxic agents or ischemia, carries a more benign prognosis, with mortality rates ranging from 7% to 26%.[5,6] Nevertheless, prevention is preferable, and determining which patients are susceptible to renal failure before a surgical procedure allows a physician to correct reversible conditions and anticipate potential problems.

Patients with chronic advanced renal failure (creatinine clearance 10 to 25 ml per minute) frequently have extrarenal manifestations of their renal dysfunction that could complicate a procedure and are at high risk for fluid, electrolyte and drug imbalance.

The prevention of acute renal failure and the care of surgical patients with established renal failure require the close cooperation of internists, surgeons and anesthesiologists. Patients already receiving hemodialysis should be followed by a nephrologist. In this article, we discuss the evaluation of renal function in surgical patients, the prevention of acute postoperative renal failure and the management of patients following an operation who have established renal disease and who are not yet receiving dialysis.

Evaluating Renal Function in Surgical Patients

Preexisting renal disease is thought to increase the risk of postoperative decline of renal function. As patients with significant renal disease may be asymptomatic, preoperative screening for renal function is mandatory. A urinalysis is useful to discover renal abnormalities. An inappropriately low specific gravity may hint at tubular dysfunction. The presence of hemoglobin on a dipstick examination may indicate hemoglobinuria or myoglobinuria, with their attendant risks of renal failure. The presence of erythrocytes, erythrocyte casts, leukocytes, leukocyte casts or bacteria may suggest glomerulitis, vasculitis or infection. Because urinary infection can be a source of graft or prosthesis infection or sepsis and can impair renal function in patients with underlying renal disease, it should be adequately treated before an elective operation. The blood urea nitrogen level is affected by volume status, urine flow and protein intake and is not a reliable indicator of renal function. The serum creatinine value is more accurate, though it does vary directly with muscle mass and also may be disproportionately elevated in patients with major muscle trauma.[7] The glomerular filtration rate (GFR) declines with age, but so does muscle mass. Therefore, while a serum creatinine level of 1 mg per dl may reflect a creatinine clearance of 120 ml per minute in a normal 20-year-old patient, it usually reflects a creatinine clearance of only 60 ml per minute in an 80-year-old person with the muscle wasting of normal aging. In pregnancy the serum creatinine level decreases due to a physiologic increase in the GFR with a constant production of creatinine. Thus, serum creatinine values considered normal in nongravid women may indicate renal insufficiency in pregnancy. Creatinine clearance can be a reliable test of renal function, but requires several hours of accurate urine collection. A quick estimate of the glomerular filtration rate may be obtained by the following formula: creatinine clearance = (140 − age) × (weight in kg)/72 × serum creatinine level (mg per dl).[8] The accuracy of this estimate depends on stable renal function and a normal relationship between weight and muscle mass. For example, patients with significant obesity or ascites excrete less creatinine per kilogram total body weight than expected. In these patients the use of an ideal predicted body weight is recommended.

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Preventing Acute Postoperative Renal Failure

Table 1 lists major risk factors for postoperative acute renal failure.

Fluid Balance

Oliguria may reflect intravascular volume depletion, hypotension, decreased cardiac output, obstruction or intrinsic renal disease. Surgical patients should have frequent monitoring of fluid intake and output, postural vital signs and prompt replacement of fluid losses. In a patient with oliguria (less than 500 ml per 24 hours of urine output), obstruction is most readily ruled out by catheterizing the bladder and doing a sonogram of the kidneys and ureters. In the absence of obstruction, a high urine specific gravity and low urine sodium level suggest prerenal causes. Other, more sophisticated indices of renal failure such as the fractional excretion of sodium and urine-to-plasma creatinine ratio may be helpful to distinguish prerenal from renal azotemia.[9]

For patients at high risk of postoperative renal failure, some authors recommend the prophylactic preoperative use of diuretics,[10] though this is controversial. There are no large prospective trials establishing a role for the use of mannitol or furosemide in preventing renal failure, and it is unclear whether diuretics offer advantages over volume repletion in preventing acute renal failure. Certain case reports and clinical trials support the beneficial effect of mannitol in surgical procedures with high risk of renal failure such as open heart,[11] complicated biliary[12] and major vascular operations.[13] Other clinical studies in similar settings have not found mannitol to be of benefit.[14,15] Also controversial is whether administering diuretics reverses incipient oliguric renal failure. Clinical studies on the benefit of furosemide in established renal failure have come to opposite conclusions, some showing benefit and others not.[16] Similarly, the beneficial effect of diuretics in patients with crush injuries has not been firmly established. In this controversial area, it seems reasonable to follow the practical advice of Levinsky and co-workers as outlined in Table 2.[17] When using these agents, care must be taken to avoid volume depletion. Patients who receive mannitol without response should be assessed for signs of volume overload as this hypertonic drug will draw fluid into the intravascular space.

TABLE 1.—*Risk Factors for Postoperative Acute Renal Failure*

- Preoperative Risk Factors
  - Preexisting renal disease
  - Volume depletion
    - Decreased effective blood volume
      - Congestive heart failure
      - Nephrotic syndrome
      - Cirrhosis
      - Hypotension
    - Volume depletion due to disease state
      - Burns
      - Trauma
      - Gastrointestinal bleeding
      - Pancreatitis
      - Acute surgical abdomen
      - Vomiting
      - Osmotic diuresis (glucose, urea)
    - Volume depletion due to iatrogenic causes
      - Diuretics
      - Fasting
      - Osmotic diuresis (mannitol, contrast dye studies)
      - Bowel preparations
      - Nasogastric suction
  - Nephrotoxic agents
      - Exogenous—drugs, contrast dyes
      - Endogenous—hemoglobin, myoglobin
  - Obstructive jaundice
- Intraoperative Risk Factors
  - Anesthesia
  - Cardiopulmonary bypass
- Postoperative Risk Factors
  - Infection—systemic, intra-abdominal

TABLE 2.—*Proposed Uses of Mannitol and Furosemide*

- In patients with crush injuries, hemolysis, acute uric acid loads
  - Fluids given intravenously
  - Mannitol or furosemide given to maintain urinary flow rates of 2 to 4 liters a day for 2 to 3 days.
- In patients with nonobstructive postoperative oliguria
  - Fluids given intravenously until a patient is euvolemic
  - If still oliguric, a trial of mannitol (12 to 25 grams) or furosemide (80 to 320 mg) given intravenously

In addition to hydration and diuretics in patients with crush injuries, alkalinizing the urine with the use of sodium bicarbonate has been recommended to enhance the rate of excretion of myoglobin and minimize its toxicity.[18] The efficacy of the use of bicarbonate remains controversial, however.[19] Large doses may fail to alkalinize the urine, and alkalemia, if achieved, could theoretically enhance deposition of calcium salts into muscle, leading to tetany.

Nephrotoxins

Because there are excellent reviews of agents known to cause renal failure,[20,21] only a few examples most pertinent to surgical patients will be discussed here.

Radiocontrast dye. The incidence of radiocontrast dye-induced nephropathy is unknown. Most experts agree that patients at increased risk of this complication include the elderly, those with preexisting renal disease or volume depletion or patients exposed to repeated doses of contrast over a short time interval.[22] The underlying reason for an operation and overall health of a patient also determine outcome. Although diabetes mellitus has been held to be a risk factor for dye-induced renal failure, recent work suggests that most nonazotemic patients with diabetes have no significant renal decline after contrast has been given,[23] though diabetic persons with renal insufficiency (creatinine level greater than 2 mg per dl) are clearly at high risk.[24] In these vulnerable patients, procedures that do not use dye, such as ultrasound, should be used if at all possible. If more than one dye study is required, they should be scheduled as far apart as possible. Hypovolemia should be avoided by limiting preparatory fluid restriction or laxative use, and, in fact, hydration with a saline solution given intravenously for several hours before the procedure is frequently indicated to ensure adequate intravascular volume and renal perfusion. Because contrast agents produce an osmotic diuresis, the urine output should be monitored and volume loss replaced after the procedure. The serum creatinine level should be measured 24 to 48 hours after the procedure to screen for contrast nephropathy.

Aminoglycosides. The incidence of aminoglycoside nephrotoxicity is recently reported to be from 8% to 26%.[25] It usually presents as nonoliguric renal failure about five to seven days after initiation of the drug regimen. Often the renal

failure is mild and reverses with discontinuation of the therapy. Patients getting aminoglycosides are frequently of advanced age or have prior renal disease or volume depletion or are concurrently using other nephrotoxic drugs. The relative importance and potential for interaction of these factors has not been established.[20] The presence of hypotension or sodium depletion enhances aminoglycoside toxicity in animals and may do so in humans. Furosemide, in the absence of volume depletion, probably does not potentiate aminoglycoside renal failure, but furosemide and aminoglycosides are both ototoxic. This is of particular concern in elderly patients in whom some degree of eighth nerve compromise may already exist. The combination of cephalothin and aminoglycoside may be more nephrotoxic than penicillin and aminoglycoside,[26] and though there are insufficient data on the newer generation cephalosporins, it would seem prudent to avoid the cephalosporin-aminoglycoside combination if possible in high-risk patients. Liver disease has recently been shown to be a risk factor for aminoglycoside renal failure.[27] Because elevated peak and trough aminoglycoside levels are associated with renal toxicity, all patients should have these measured on the third day and monitored, along with serum creatinine levels, thereafter.

Nonsteroidal anti-inflammatory drugs. The physiologic effects of renal prostaglandins remain incompletely defined.[28] They appear to antagonize the vasoconstrictive effects of angiotensin or norepinephrine released during renal ischemia, thus maintaining renal blood flow and the GFR. Nonsteroidal anti-inflammatory drugs, by blocking prostaglandin-mediated vasodilatation, lead to unopposed renal vasoconstriction, hypoperfusion and a decreased GFR. These drugs may cause a reversible decrease in renal function when given to patients with volume depletion, intrinsic renal disease, congestive heart failure, the nephrotic syndrome or cirrhosis.[28] They should not be used in surgical patients with renal disease or the potential for renal ischemia. To minimize the risk of renal injury, it may be prudent to discontinue the use of these agents in all patients a few days before a nonemergency operation.

Obstructive Jaundice

For uncertain reasons, patients with obstructive jaundice preoperatively are at high risk for having postsurgical renal failure and complications not seen in nonjaundiced patients who have postoperative renal failure.[10] Uremia aggravates the complications of obstructive liver disease by increasing the pool of urea available for degradation to ammonia in the gut, increasing bleeding due to functionally inactive platelets and increasing the risk of infection. In these patients renal failure may cause the bilirubin level to rise to a level deleterious to body tissues. Because surgical intervention is often required in a patient with obstructive jaundice, scrupulous attention to renal function is required.

Anesthesia

All general anesthetics appear to decrease renal blood flow in proportion to the depth of anesthesia.[28] Spinal anesthesia in humans causes only a slight change in renal blood flow and renal vascular resistance.[29] The general anesthetic methoxyflurane is inherently nephrotoxic, as its metabolite fluoride may induce a nephrogenic diabetes insipidus and renal failure.[30] Methoxyflurane toxicity is in part dose-related and may be potentiated by the use of phenobarbitol, aminoglycosides and tetracycline. Enflurane also produces fluoride as a metabolite and can induce a diabetes insipidus-like state.[31] It would be prudent to avoid administering this drug to patients with preexisting renal disease or a prior history of methoxyflurane renal toxicity.

TABLE 3.—*Guidelines for Drug Therapy in Patients With Renal Failure*

Use a drug only if specifically indicated
Select a drug with the least renal excretion
Refer to published dosing guidelines for renally excreted drugs
Observe blood concentrations if available and known to be accurate
Check medication list if an adverse reaction of any kind develops
Realize that hepatic dysfunction may decrease a drug's excretion by an alternate route

Cardiopulmonary Bypass

A cardiopulmonary bypass operation decreases the GFR by about 30% and the renal plasma flow by 25%.[32] This decrease in renal function results from the combined effects of anesthesia, hypothermia, decreased mean arterial pressure, metabolic acidosis and nonpulsatile blood flow. Erythrocytes damaged by the bypass machine release vasoconstrictor substances. The most important risk factor for renal failure may be the duration of extracorporeal circulation.

Infection

Uncontrolled local or systemic infection predisposes surgical patients to renal failure,[33] a result of associated hypotension, vasoconstriction, disseminated intravascular coagulation and nephrotoxic antibiotic therapy.

Caring for Surgical Patients Who Have Advanced Renal Disease

Patients with advanced renal failure (creatinine clearance of 10 to 25 ml per minute) but who are not yet receiving dialysis are often managed conjointly by their general internist and surgeon. Obviously those factors that predispose to acute renal failure in any surgical patient must be assiduously avoided in this vulnerable population. Accurate mortality statistics for surgical patients in this category are, however, unavailable. To assure the best care, particular attention must be paid to drug use, fluid and electrolyte balances, acid-base status, anemia, metabolic-nutritional state and infection.

Drug Use

Adverse drug reactions are common in patients with advanced renal disease.[34,35] Drug toxicity may occur when renally excreted drugs such as digoxin or drugs with renally cleared active metabolites such as meperidine (Demerol) hydrochloride are given without adjusting for compromised renal function. Uremia alters the protein binding of certain drugs and thus can affect total and unbound drug concentrations.[36] Serum phenytoin levels, for example, are notoriously unreliable in cases of uremia, and patients with "normal" levels in the laboratory may have a toxic reaction. The use of sodium- or potassium-containing antibiotics, innocuous in normal patients, can cause volume overload or hyperkalemia in patients with renal disease. When using drugs in patients with renal failure, following certain principles will minimize complications (Table 3). The level of renal function, estimated by the creatinine clearance (see section on evaluation of renal function), is the basis for calculating drug dosing. A standard initial dose should be given when it is important to

reach a therapeutically effective concentration in the shortest time possible, such as when using antibiotics. Maintenance doses are then adjusted by changing either the dosing interval or the dose of the drug. For drugs excreted entirely by the kidneys, either of the following formulas can be used as an initial guide. Because no controlled clinical trials have been done to establish their comparative efficacy or toxicity, the choice of methods depends primarily on which gives the more convenient dose or administration schedule.[37]

Dosing interval for patients with renal failure:
Normal dosing interval × (normal creatinine clearance/patient's creatinine clearance).

Dose for patients with renal failure:
Normal dose × (patient's creatinine clearance/normal creatinine clearance).

Dosing guidelines for many drugs are readily available in the literature.[38]

Fluid Balance

A common cause of deteriorating renal function in surgical patients with renal disease is fluid depletion. Volume deficiency may not be evident on physical examination and measuring urine and serum sodium levels is not always helpful, as they may be either high or low in these patients. A fluid challenge may be warranted, and consideration should be given to measuring through a Swan-Ganz catheter in patients whose volume status is uncertain. Decreasing renal function may also signal the presence of congestive heart failure, and because this is a major surgical risk factor,[39] nonemergency surgical procedures should be postponed for several days while a patient is treated with appropriate drugs or dialysis.

Preoperative hypertension usually results from fluid overload and responds to diuresis with a potent drug such as furosemide. Thiazides are ineffective in patients with a creatinine clearance of less than 30 ml per minute, and potassium-sparing diuretics such as triamterene are both ineffective and associated with the risk of serious hyperkalemia. When therapy with a second drug is indicated, hydralazine hydrochloride is particularly useful because it has a rapid onset and can be given parenterally. The data of Goldman and Caldera[40] suggest that no benefit accrues from postponing an operation solely to control the blood pressure in patients whose diastolic blood pressure is less than 110 mm of mercury. Patients with underlying hypertension remain at about 25% risk of intraoperative hypertension or hypotension even with preoperative normalization of blood pressure. It is safe and desirable to continue a patient's regular antihypertensive medication regimen up to and including the morning of a procedure and resume it immediately after the operation.[41]

Intraoperative hypotension occurs mostly in patients who are dialyzed, with fluid removal, less than 24 hours before an operation, who are receiving antihypertensive drugs or who have a kidney removed that was a major source of preoperative hypertension. Swan-Ganz monitoring intraoperatively of such unstable patients is warranted.

Hypertension or congestive heart failure (or both) may develop during the second or third postoperative day as fluid is mobilized intravascularly from interstitial tissues. It should be watched for and vigorously treated, principally with diuretics.

Electrolyte Balance

Hyponatremia occurs commonly in patients with renal disease and can be due to a variety of disorders. Because treatment varies significantly, it is important to determine a cause (Figure 1). The first step is to calculate or measure serum osmolality. A simple calculation is 2 (serum sodium + potassium) + (serum urea/2.8) + (serum glucose/18). Hyponatremia, with normal or high serum osmolality, may be due to hyperlipidemia, hyperglycemia or hyperproteinemia. Other hyponatremic conditions are associated with hypotonicity, where the total body water level is inappropriately high with respect to the total body sodium level. The extracellular fluid volume should be clinically assessed in these patients with vital signs, intake and output records, skin turgor and neck veins. The usual laboratory tests of volume may be difficult to interpret in patients with renal disease whose serum hematocrit is usually decreased, urea and creatinine concentrations increased and ability to concentrate urine impaired.

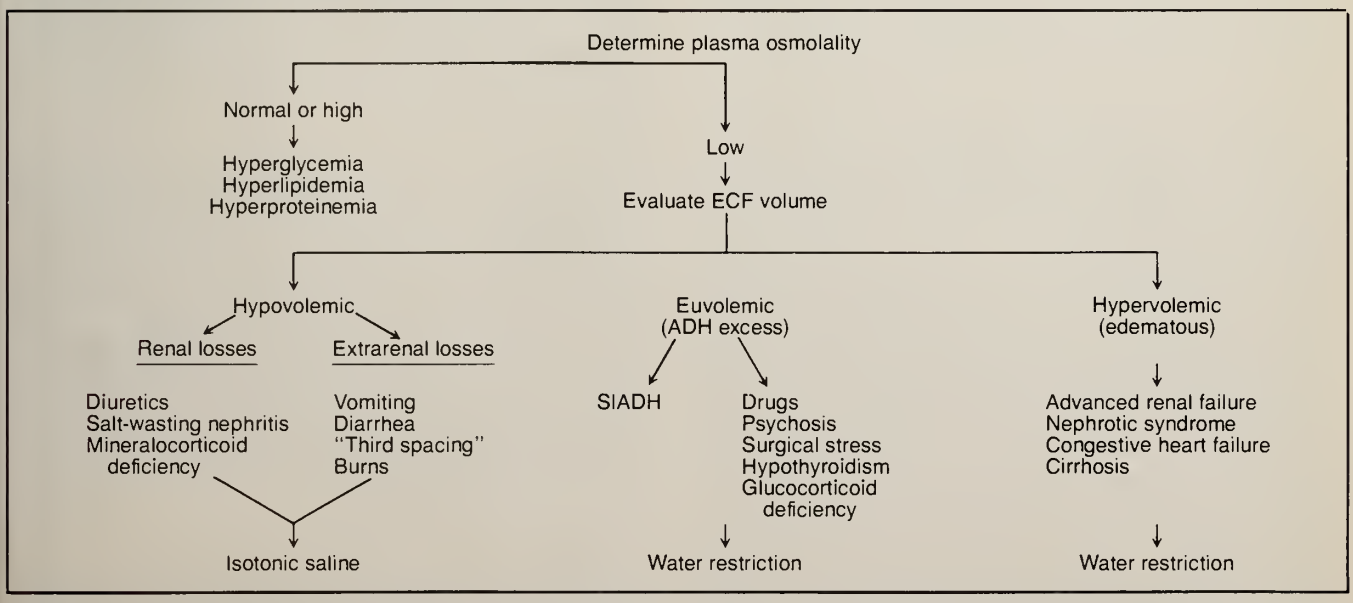

Figure 1.—Diagnostic approach to hyponatremia. ADH = antidiuretic hormone, ECF = extracellular fluid, SIADH = syndrome of inappropriate [excretion of] ADH

In patients with renal failure, hyponatremia is usually associated with excess total body sodium levels because the ability to excrete free water diminishes as the kidneys fail. This may be exacerbated by a surgically stimulated release of pituitary antidiuretic hormone.[42] Restricting free water will correct hypervolemic hyponatremia. Hyponatremia associated with volume depletion can develop in a patient with renal failure due to any factor that causes a proportionately greater loss of sodium than water, including overzealous diuretic use, vomiting, diarrhea, "third spacing" or osmotic diuresis from the use of mannitol, urea or glucose. This is compounded by a diseased kidney's inability to rapidly decrease sodium excretion. Patients with a GFR of 10 to 15 ml per minute whose sodium intake is severely restricted may be unable to reduce sodium excretion to equal the sodium intake even after two to three weeks. In surgical patients euvolemic hyponatremia usually results from excessive use of hypotonic fluids and antidiuretic hormone excess from drugs, surgical stress or the syndrome of inappropriate antidiuretic hormone excretion. Restricting free water is the treatment of choice. To avoid central nervous system complications, it is prudent to treat all patients whose serum sodium level is less than 125 mEq per liter. It is recommended that the preoperative level be raised to a minimum of 131 mEq per liter.[43]

Many factors cause hyperkalemia in surgical patients with renal disease (Table 4). Hyperkalemia may develop intraoperatively if patients are not hyperventilated to maintain their habitual respiratory compensation for underlying metabolic acidosis, or postoperatively if their endotracheal tube is removed too soon or if they are kept heavily sedated. Hyperkalemia is a risk factor for postoperative death from ventricular arrhythmias,[44] and it is important to lower the serum potassium level to less than 5 mEq per liter before a surgical procedure to give a safe margin for a possible rise in the potassium level during the intraoperative or immediate postoperative period. In urgent situations (serum potassium level greater than 7.5 mEq per liter or electrocardiographic changes of hyperkalemia), a regimen of calcium gluconate, insulin plus glucose or sodium bicarbonate given intravenously lowers potassium levels immediately for one to two hours. A cation-exchange resin (sodium polystyrene sulfonate [Kayexalate]) given orally or rectally works more slowly but removes potassium from the body. Kayexalate exchanges sodium for potassium so should be used with caution in patients at risk for volume overload. Hemodialysis is an effective definitive treatment when the above measures cannot be used. Preoperative hypokalemia in these patients is less common, but should it occur, replacement must be given slowly and monitored carefully with serum potassium levels measured frequently.

TABLE 4.—*Common Causes of Hyperkalemia in Surgical Patients With Chronic Renal Failure*

Exogenous
Total parenteral nutrition
Potassium supplements
"Co-salt" (salt substitute containing potassium chloride)
Blood transfusion
Potassium-containing drugs, including antibiotics
Respiratory depressants that compromise compensatory hyperventilation
Endogenous
Hemolysis
Reabsorption of hematoma
Rhabdomyolysis
Tissue trauma
Metabolic acidosis
Cell-membrane depolarizing drugs, such as succinylcholine chloride
Failure to appropriately hyperventilate

Metabolic Acidosis

Metabolic acidosis, common in renal failure, predisposes patients to arrhythmias during an operation. Surgical patients may suffer superimposed lactic acidosis, ketoacidosis or the loss of their compensatory hyperventilation as described. In these patients, the serum bicarbonate level may drop to as low as 5 mEq per liter. Any reversible process should be identified and corrected, and the serum bicarbonate level should be raised to 15 mEq per liter; levels above this add very little to the physiologic function.[44] This can be done using the following formula as a guide: mEq of sodium bicarbonate required $= 0.5 \times$ total body weight in kg $\times$ (15 $-$ bicarbonate measured). If a patient with acidosis has volume overload or hypernatremia, dialysis is indicated.

Anemia

Patients with chronic renal failure are generally well adapted to their anemia, and presurgical transfusions are usually unnecessary.[45,46] Patients with less than 7 to 8 grams of hemoglobin who are elderly or have coronary artery disease may be symptomatic and benefit from transfusions. To minimize volume overload and hyperkalemia, transfusions should be with fresh or fresh-frozen packed erythrocytes. Patients who are euvolemic before a transfusion should be given furosemide intravenously with each transfusion to avoid precipitating congestive heart failure.

Hypercatabolism

Disorders requiring a surgical procedure and the procedure itself induce a catabolic state that quickly becomes apparent in patients with limited renal reserve. The potential for malnutrition due to restricted "renal failure" diets, increased metabolic needs and gastrointestinal dysfunction must be anticipated. Clinical surgical experience suggests that parenteral nutrition can reduce complications and improve survival in selected surgical patients.[47]

Infection

Infection occurs in as many as 32% of surgical patients with renal failure,[45,46] often with significant prolongation of the hospital stay. The lungs, the wound and the genitourinary tract remain the most frequent sites, and infection of the genitourinary tract may cause further deterioration of renal function by inflammation or functional obstruction. Infection should be aggressively prevented, with emphasis given to nutritional support, early ambulation, scrupulous pulmonary toilet and minimizing the use of invasive instruments, especially urethral catheters. No data exist proving the efficacy of routine antibiotic prophylaxis solely for renal failure, and this practice is not recommended.

Summary

Patients in whom acute postoperative renal failure develops have a high mortality despite progress in supportive therapy. The most effective method of prevention is to recog-

nize and modify, if possible, any predisposing factors. General internists, surgeons and anesthesiologists must also deal with patients who have established renal failure. These surgical patients often have many associated medical problems and tenuously balanced metabolism. Awareness of frequently occurring problems and conditions that lead to worsening renal failure in surgical patients will minimize complications and preserve the remaining renal function.

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Acute Promyelocytic Leukemia

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Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia frequently associated with disseminated intravascular coagulation (DIC). Data on 11 patients with APL treated at our institution were analyzed and compared with those of 147 published cases. Most had a bleeding diathesis at presentation and evidence of DIC eventually developed in all. Seven patients (64%) showed the t(15;17)(q22;q21) karyotype or a similar translocation. Using a chemotherapy induction regimen containing an anthracycline, complete remission, requiring a total of 14 courses of treatment, was achieved in six patients (55%). The median duration of response and median survival for complete responders were 10 and 15 months, respectively. Three patients (27%) died of bleeding complications during induction therapy. The tritiated-thymidine labeling index of leukemia cells predicted which patients would achieve a complete remission. Review of six studies of 147 patients with APL from the past 12 years supports the use of a chemotherapy induction regimen containing anthracycline or amsacrine and heparin for the treatment of DIC.

(Kingsley EC, Durie BGM, Garewal HS: Acute promyelocytic leukemia. West J Med 1987 Mar; 146:322-327)

Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia (AML) characterized by proliferating abnormal promyelocytes. Most patients with this disorder present with a hemorrhagic diathesis usually associated with disseminated intravascular coagulation (DIC). It is often difficult to successfully induce remission because of DIC-associated hemorrhagic complications, particularly cerebral hemorrhage. Baker and co-workers were the first to report more than 20 years ago the successful use of heparin in the treatment of DIC in a patient with APL.[1] Eight years later Gralnick and associates confirmed the beneficial effects of using heparin in three patients with APL.[2] Since that time no prospective randomized study has been carried out, and recently some investigators have questioned the efficacy of using heparin in treating this disorder.[3] There is, therefore, still some controversy regarding the ideal supportive measures necessary for inducing remission in APL.

Another characteristic of APL, reported by some investigators, is a survival advantage for complete responders when compared with other subtypes of acute myelogenous leukemia.[4-6] This possible survival advantage theoretically would offset the increased number of early deaths associated with DIC-related hemorrhagic complications occurring during induction chemotherapy, resulting in long-term survival rates comparable to those seen with other subtypes of acute myelogenous leukemia.

A third purported characteristic of APL is an apparent resistance to standard chemotherapy in some patients.[7] Bernard and colleagues first showed a definite therapeutic efficacy with the use of daunorubicin hydrochloride in this disorder.[6] This was later confirmed by others.[4,8] Several authors, however, noted that many patients require several courses of chemotherapy to induce remission.[6,7] But investigators more recently have emphasized that complete remission in patients with APL can occur without marrow aplasia and that a pattern of leukemic cell differentiation may occur.[4,9,10] This is obviously a very important point in initially monitoring patients.

In this review we evaluate our experience with APL and contrast and compare our findings with those published in the literature with respect to the three specific issues introduced above. We also make detailed recommendations regarding the treatment of the DIC associated with APL. The possible role of a pretreatment tritiated-thymidine labeling index of leukemic cells as a prognostic factor in this disorder is discussed.

Methods

Eleven previously untreated patients with APL who received induction chemotherapy within the past seven years at the University Medical Center of the University of Arizona College of Medicine, Tucson, are described. The diagnosis of APL was made on the basis of pretreatment blood smears, bone marrow aspiration and biopsy and cytogenetic findings. Our criteria for APL are those of the French-American-British cooperative group.[11] The one-stage prothrombin time (PT) was determined using dried rabbit brain thromboplastin with calcium (Thromboplastin C, Dade Diagnostics, Inc, Aguada, Puerto Rico), and an activated partial thromboplastin time (PTT) was measured using liquid rabbit brain cephalin with plasma activator (Actin, Activated Cephaloplastin Reagent, Dade Diagnostics, Inc). Fibrinogen levels measured using Data-fi Thrombin Reagent (Dade Diagnostics, Inc) and fibrin- and fibrinogen-degradation products were measured using the Thrombo-Wellcotest (Wellcome Diagnostics, Dartford, England). The above coagulation tests

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ABBREVIATIONS USED IN TEXT

AAT = amsacrine, ara-C (cytarabine) and thioguanine
AML = acute myelogenous leukemia
APL = acute promyelocytic leukemia
DAT = daunorubicin hydrochloride, ara-C (cytarabine) and thioguanine
DIC = disseminated intravascular coagulation
PT = prothrombin time
PTT = partial thromboplastin time

were done at the time of diagnosis and generally two to three times a day while patients were receiving heparin. The tritiated-thymidine labeling index was determined as previously described,[12] using bone marrow cells obtained before initiating induction chemotherapy. Leukemic promyelocytes plus blasts were counted for labeling.

All patients were treated with anthracycline or cytarabine institutional chemotherapeutic protocols for acute nonlymphocytic leukemia (see Table 1). DIC was defined as the presence of fibrinogen-split products at a level of 40 mg per dl or more with a low fibrinogen level (normal 150 to 400 mg per dl). Specific factor assays were not routinely done. All patients (except patient 2) were given heparin, which therapy was begun immediately before initiating chemotherapy. A loading dose of 5,000 units was administered as a bolus followed by a continuous infusion, initially at 7 to 10 units per kg body weight per hour. The heparin infusion was adjusted to maintain a fibrinogen level greater than 100 mg per dl. Patients continued to receive heparin until the coagulopathy resolved, which occurred as the leukemia went into remission. If fibrinogen levels were not corrected by heparin therapy alone without excessive prolongation of the partial thromboplastin time or were low to begin with, then cryoprecipitate was administered. Platelet transfusions were administered to maintain platelet counts above 30,000 per μl.

All patients were treated under conditions of reverse isolation. Laminar flow rooms were not routinely used. Fever and infection were treated aggressively in the usual manner by administering broad-spectrum antibiotics (generally, an aminoglycoside plus cephalosporin), with antifungal agents being added as needed. Two patients received granulocyte transfusions.

The criteria for complete remission were fewer than 5% myeloblasts in bone marrow specimens with morphologically normal-appearing promyelocytes and normal recovery of all elements. Coagulation test findings had to be normal. The duration of survival was calculated from the date of diagnosis (usually within a few days of the start of treatment).

Results

UMC Experience

A total of 11 patients with APL received treatment at the University Medical Center within the past seven years (Table 1). Four patients (36%) were male and the median age at diagnosis was 28 years. Most patients presented with a bleeding diathesis and all but one had laboratory evidence of DIC. DIC developed in that patient, however, when induction chemotherapy was begun. The median leukocyte count was 3,800 per μl with 73% (eight) of the patients having leukocyte counts less than 20,000 per μl. The median peripheral myeloblast count was 2%, promyelocytes 22% and neutrophils 7%. The median hemoglobin was 10.1 grams per dl. The median platelet count was 21,000 per μl, with 82% of the patients having counts less than 50,000 per μl. Five of eight patients in whom adequate karyotype determinations could be done showed the typical t(15;17)(q22;q21), or a similar translocation, before treatment. Six patients (55%) had complete remission; patient 5 required a single course of induction chemotherapy; patients 7, 8 and 9 received two courses; patient 10 received three courses, and patient 11 received four courses. Median survival was six months for all patients. The median duration of response and median survival for complete responders were 10 months and 15 months, respectively. Figure 1 shows the actuarial survival of all 11 patients. Three patients (27%) are alive and free of disease at 14, 31 and 80 months. If the single patient not treated with heparin (patient 2) is excluded from analysis, then 60% of our patients achieved a complete response, with a median survival of eight months.

Patients 1, 4 and 7 (27%) died of hemorrhage. All three hemorrhagic deaths (two from cerebral hemorrhage and one from gastrointestinal tract and pulmonary hemorrhage) oc-

TABLE 1.—*Patient Characteristics and Treatment Response at the University Medical Center, Tucson*

Patients	Age, Yr	Karyotype	Number of Induction Courses*	Response	Survival, Mo	Cause of Death
1	22	t(15;17)(q22;q21)†	1	Died	0.5	Subdural hematoma associated with DIC; persistent APL
2	2	t(15;17)(q22;q21)	1	Died	0.5	Sepsis, persistent APL
3	30	t(15;17)(q22;q21)†	1	CR	17	Sepsis, relapse APL
4	39	Normal	1	Died	0.5	GI tract and pulmonary hemorrhage associated with DIC; persistent APL
5	46	t(15;17)(q22;q21)	1	CR	13	Uncertain; APL relapse
6	51	t(15;17)(q22;q21)	1	Died	0.3	Sepsis, persistent APL
7	28	t(15;17)(q22;q21)	2	Died	0.1	Subdural hematoma associated with DIC; persistent APL
8	35	Normal	2	CR	72+	-----
9	22	Not determined	2	CR	27+	-----
10	23	Not determined	3	CR	10+	-----
11	18	t(15;17)(q22;q21)	4*	CR	13	Sepsis, relapse APL

APL = acute promyelocytic leukemia, CR = complete remission, DIC = disseminated intravascular coagulation, GI = gastrointestinal

*2 courses of a combination of anthracycline and cytarabine, plus 2 courses of a combination of BCNU (carmustine), cyclophosphamide (Cytoxan), vincristine sulfate, prednisone, methotrexate and methyl-glyoxal *bis*-guanylhydrazone (MGBG).

†In two patients, the karyotype was not found before treatment was started, but following relapse.

curred within 18 days of beginning induction chemotherapy. Patients 2, 3, 6 and 11 (36%) died of infection. Patient 11 died of infection during a relapse seven months after achieving a complete remission. Although the cause of death of patient 5 was unknown, there was no evidence of hemorrhage at the time of death. Persistent leukemia was present at the time of death in all eight patients. On evaluating the three patients who died of bleeding complications (1, 4 and 7), we found that two had active DIC at the time of death. The third patient had prolonged prothrombin and partial thromboplastin times but a normal fibrinogen level and no fibrin- or fibrinogen-split products. All three patients were receiving heparin, cryoprecipitate and platelet transfusions.

Most of our patients required escalation of the heparin dose to approximately 15 units per kg per hour and administration of large daily doses of cryoprecipitate (occasionally as many as three doses per day) to maintain fibrinogen levels of greater than 100 mg per dl. This was particularly the case during the first week of induction chemotherapy when DIC was the most severe.

Labeling index data were evaluated for two response categories designated A and B (Figure 2). Group A patients are those who achieved a complete remission, while group B patients are those who died within one month of the test without achieving a complete remission. Patients 3 and 5 achieved a complete remission initially, but later relapsed and died. Thus, they are included in both groups. Overall, the labeling index was lower in patients achieving a complete remission than in those who did not (Figure 2; $P = .06$). In group A, patient 5 required one course; patients 3, 8 and 9 required two courses of chemotherapy, and patient 10 three courses to achieve complete remission. In group B, patients 1 and 6 died of subdural hematoma and sepsis, respectively, with resistant APL within three weeks of receiving one course of chemotherapy. Patients 3, 5 and 11 all died in relapse after several chemotherapeutic regimens failed. Both patients 3 and 5 had higher labeling index values at relapse than earlier in their course.

Analysis of Previously Published Cases

Review of the literature showed that at least six studies of seven or more adult patients with APL have been published within the past 11 years (Table 2). A total of 147 patients from these studies was treated for their disease and their cases are, therefore, analyzed here. Two additional recent studies, presented only in abstract form, were excluded from this detailed analysis because much of the information required was not available.[9,10] Cases were stratified by type of induction chemotherapy given (± anthracycline) and by type of treatment for DIC (± heparin).

Only three of the six studies contain detailed data on DIC therapy. Collins and co-workers administered continuous infusions of heparin at 10 units per kg per hour without a loading dose. The heparin dose was adjusted to maintain the thrombin time between 20 and 60 seconds. Patients received heparin until the coagulopathy "demonstrated slowing." Cryoprecipitate was transfused to maintain the fibrinogen level at greater than 250 mg per dl. Fresh frozen plasma was given to maintain a factor V level at greater than 50%. Vitamin K and platelets were also administered. Drapkin and associates[14] and Arlin and colleagues[15] administered a continuous heparin infusion at 5 to 10 units per kg per hour for 5 to 14 days. The heparin dose was increased until "therapeutic levels were established," usually at 10 to 20 units per kg per hour. Coagulation factors were replaced with fresh frozen plasma and platelets were administered once or twice a day. Sufficient data concerning heparin treatment were available for a total of 60 patients. In all, 32 received heparin, of which 24 (75%) achieved a complete remission. Median survival for these patients was 15.0 months. Four (13%) died of DIC-related complications. Of the 28 who were not treated with heparin, 10 (36%) achieved a complete remission. Median survival for these patients was 0.8 months, which is signifi-

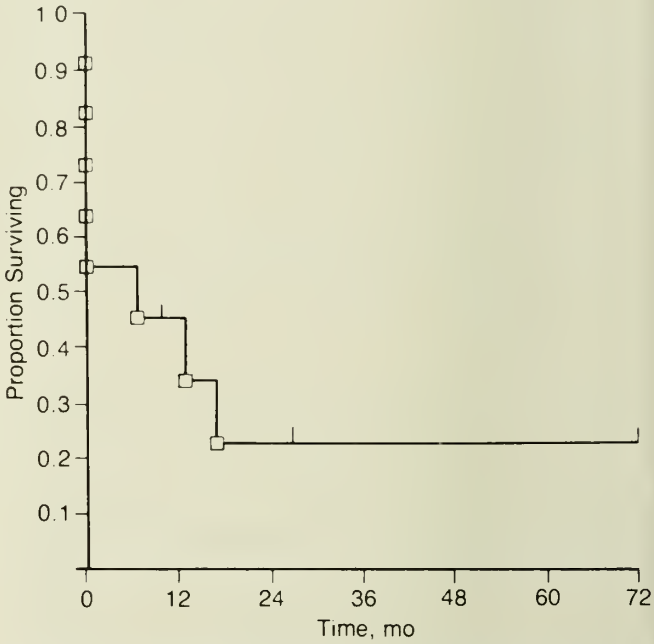

Figure 1.—Actuarial survival of all 11 patients treated at the University Medical Center of the University of Arizona College of Medicine, Tucson.

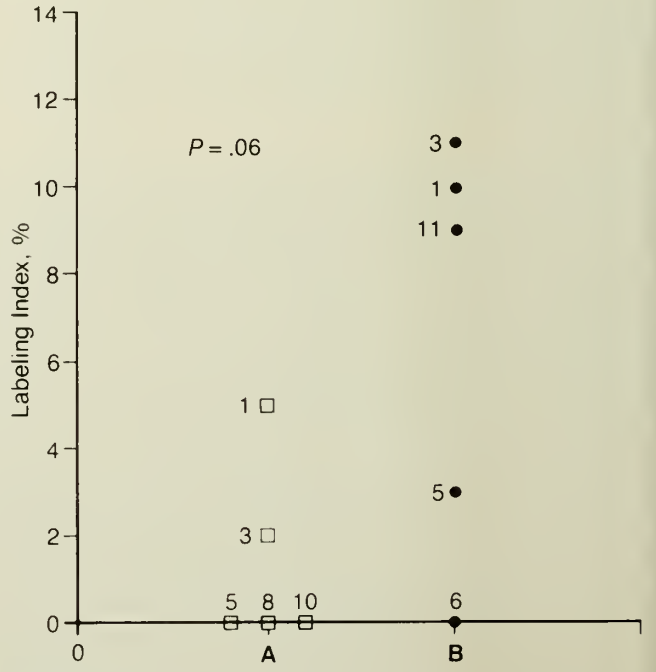

Figure 2.—Tritiated-thymidine labeling index of marrow blasts in acute promyelocytic leukemia. Group A patients (□) all had a complete remission. Group B patients (●) died of hemorrhagic complications with persistent acute promyelocytic leukemia. The patient number appears next to the labeling index value.

cantly less ($P = .019$) than the median survival of patients treated with heparin. There were 13 deaths related to DIC complications, which accounted for a total of 47% of the entire group, a figure significantly greater than that for patients treated with heparin ($P = .004$).

The median age of all 147 patients was 35 years and 51% were male. The median leukocyte count was 5,500 per μl, the median hemoglobin was 8.9 grams per dl and the median platelet count was 20,000 per μl. Of 84 evaluable patients, 73% (61) had DIC as defined by each institution's criteria.

The data in Table 2 are summarized in Table 3. Of the 147 evaluable patients, 69 (47%) had a complete remission and 52 patients (35%) died of DIC-related complications. The median survival for all patients was 2.2 months. Of the 147 patients, 107 were treated with anthracycline-containing combinations. Of the 107 patients, 61 (57%) achieved a complete remission, with a median survival for all 61 patients of 4.8 months. Of the 107 patients, 22 (21%) died of DIC-related causes. Of the 40 patients treated with combinations without anthracycline, 13 (33%) achieved a complete remission. The median survival for these patients was 0.5 months. This figure is significantly lower ($P = .035$) than the 4.8 months' survival in patients treated with anthracyclines. In the group not receiving anthracycline, 31 (78%) patients died of DIC-related complications, which is significantly greater than the 21% of patients treated with an anthracycline ($P = .001$). It should be noted that most of those patients achieving a complete remission were from Arlin's study and were treated with amsacrine.

Of all 147 patients, 32 were treated with either an anthracycline- or amsacrine-containing regimen plus heparin, and 22 (69%) achieved a complete remission. The median survival for all 32 patients was 15.0 months. Four patients (13%) died of DIC-related complications.

Discussion

Comparing the courses of the patients with APL treated at the University Medical Center within the past seven years with those of patients reported in the literature shows many similarities. Our patients were, however, younger, with a median age (28 years) that was about 20 years less than that reported for other patients with this subtype of AML. Most presented with hemorrhage associated with DIC. The peripheral leukocyte count was almost always below 20,000 per μl, a previously noted characteristic of APL not often seen in patients with other AML subtypes. The median platelet count was also lower than that usually seen with other subtypes of AML, probably a result of both marrow involvement with leukemia and of platelet consumption due to DIC. Most of our patients showed the typical t(15;17)(q22;q21), or a similar translocation, characteristic for this disease.[7,16-18] Overall, 55% (six) of our patients had a complete remission with a median duration of response of ten months. The median survival was six months. Excluding the 2-year-old patient not

TABLE 2.—*Summary of Published Cases and University Medical Center, Tucson, Series*

Patients, Number	Median Age, Yr	Sex Male, %	Patients With DIC, %	Karyotype t(15;17), %	Induction Chemotherapy	DIC Treatment	Patients Achieving CR, Number (%)	Median Duration of Responses, Mo	Deaths Due to DIC, Number (%)	Median Survival, Mo	References
30	..	..	..	...	Multiple regimens	Heparin (N=9), platelets	4 (13)	2	23 (77)	..	Bernard et al, 1973[6]
33	..	..	..	...	Daunorubicin hydrochloride		19 (55)	26	"Negligible"	..	
13	35	54	64	...	Daunorubicin or doxorubicin (Adriamycin) hydrochloride	Platelets	7 (54)	4.9	4 (31)	1	Ruggero et al, 1977[13]
7	39	71	71	...	Prednisone	Cryo, heparin, platelets, FFP	5 (71)	27	1 (14)	26	Collins et al, 1978[8]
7					Thioguanine+Ara-C	None	1 (14)	72	4 (57)	1	
8	39	54	79	...	Daunorubicin+Ara-C	None	2 (25)	35	5 (56)	1	Drapkin et al, 1978[14]
9					Daunorubicin+Ara-C	Heparin	7 (78)	15	2 (22)	10	
16	31	..	75	91	AMSA or thioguanine+ Ara-C+daunorubicin	Heparin, platelets, FFP	12 (75)	10	1 (5)	..	Arlin et al, 1984[15]
21	28	56	72	100	Thioguanine+Ara-C+ daunorubicin or thioguanine+Ara-C	Heparin (N=16)	11 (52)	17	9 (43)	5	Larson et al, 1984[7]
3							1 (33)	8	3 (100)	1	
11	28	36	100	63	[See Table 1]	Cryo, heparin, platelets	6 (55)	15	3 (27)	6	Current series
Totals 158	35	55	76	90			(47)		(44)	2.2	

AMSA=amsacrine, Ara-C=cytarabine, CR=complete remission, Cryo=cryoprecipitate, DIC=disseminated intravascular coagulation, FFP=fresh frozen plasma

TABLE 3.—*Summary of Table 2 by Treatment Type*

Patients, Number	Patient Treatment Category	Complete Remission, Number (Percent)	Median Survival, Mo	P Value (for MS)	DIC Deaths, Number (Percent)	P Value (for DIC Deaths)
147	All patients	69 (47)	2.2	....	52 (35)	....
40	Without anthracycline	13 (33)†	0.5	.035	31 (78)	.001
107	With anthracycline	61 (57)	4.8		22 (21)	
28*	Without heparin	10 (36)	0.8	.019	13 (47)	.004
32	With heparin	24 (75)	15.0		4 (13)	
32	With anthracycline or amsacrine, plus heparin	22 (69)	15.0	....	4 (13)	....

DIC=disseminated intravascular coagulation, MS=median survival

*Numbers add up to less than 147 because information on therapy for disseminated intravascular coagulation is incomplete
†Most patients were treated with an amsacrine regimen.

treated with a regimen of heparin, 60% of our patients had a complete remission, with a median survival of eight months. The median survival of our patients does not differ significantly from that of cases reported in the literature in which the patients were treated with anthracycline- or amsacrine-containing regimens and heparin.

Three of our patients (27%) died of DIC-associated hemorrhage, which is higher than, but not significantly different from, the 13% of patients treated with heparin reported in the literature. The initial fibrinogen level has been noted by several investigators[6,8,13] to have prognostic significance. Five of our six patients who achieved complete remission had initial fibrinogen levels of greater than 100 mg per dl, whereas only two of the five patients who died during induction chemotherapy had fibrinogen levels greater than 100 mg per dl (data not shown; $P = .31$).

The labeling index served as a prognostic factor for our patients. With two exceptions, patients with a labeling index of 5% or less successfully achieved a complete remission. Of interest is that three of five patients with a labeling index of 5% or less still required two or more courses of chemotherapy to achieve a complete remission. Because in only one of our patients did a complete remission occur with only a single course of chemotherapy, evaluating the role of the labeling index for discriminating drug sensitivity was not possible.

One striking feature of our patient population was the apparent tumor resistance to standard chemotherapy. Only one of six patients achieving a complete remission did so with a single course of induction chemotherapy. Patients 7, 8 and 9 each required two courses of chemotherapy, patient 10 required three courses and patient 11 four courses of chemotherapy. This type of apparent drug resistance in cases of APL was also noted by Larson and co-workers.[7] Of their 13 patients, 8 showed evidence of significant drug resistance following the first course of chemotherapy and only 2 of these patients eventually had a complete remission with additional treatment. Of their entire group of 24 treated patients, 3 achieved a complete remission with one course of chemotherapy, 6 required two courses and 2 had a complete remission only after three or more courses of chemotherapy. This seeming drug resistance, however, may not be as substantial as first thought. In contrast to other subtypes of acute myelogenous leukemia, in APL *marrow aplasia may not be essential to accomplish remission.*[9,10] If significant—although perhaps not complete—cytoreduction occurs with one induction course, it may be wise to defer a second course until it is clear if remission will occur or, conversely, leukemia regrowth will ensue.

Despite the possibility of inherent drug resistance in cases of APL, it would appear that the highest rates of complete remission are achieved with the use of either amsacrine- or anthracycline-based regimens. This conclusion is supported by data recently published by Cunningham and associates in which 53 evaluable patients were treated with either daunorubicin hydrochloride, ara-C (cytarabine) and thioguanine (DAT) or AMSA (amsacrine), ara-C and thioguanine (AAT).[4] In all, 29 of 44 patients (66%) treated with DAT and 9 of 9 patients treated with AAT had a complete remission (72% total). Median survival was 15+ months. Kantarjian and colleagues also recently reported the cases of 60 patients with APL who received either amsacrine- or anthracycline-based regimens.[5] The complete remission rate was 53% and the median duration of response was 29 months. Because of the limited size of our own patient population, we could not compare overall survival of APL patients with that of other AML subtypes. A recent large, prospective European study, however, showed no significant difference in survival between the APL patients and patients with other AML subtypes.[19]

Recommendations for DIC Therapy

On the basis of our experience, we propose the following treatment protocol be used in all patients with DIC associated with APL in whom induction chemotherapy is to be given (see Figure 3). Before administering any chemotherapy, heparin should be initiated with a bolus injection of 5,000 units followed by a constant infusion of 7.5 to 10 units per kg per hour (about half the usual dose for "full" anticoagulation).

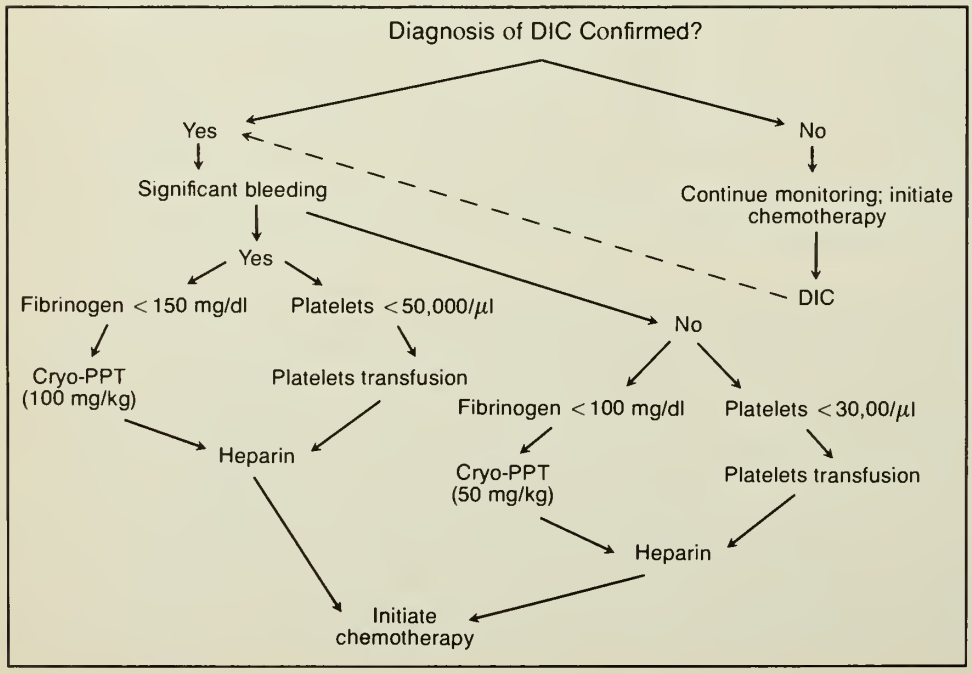

Figure 3.—The diagram shows an algorithm for the treatment of disseminated intravascular coagulation (DIC) in patients with acute promyelocytic leukemia. Where a diagnosis of DIC has been confirmed ("Yes"), most patients will have evidence of it at presentation. If not yet confirmed ("No"), coagulation variables must be monitored at least every 6 hours initially (see text). The heparin dose consists of 5,000 units initially, followed by 7.5 to 10 units per kg per hour, with the dosage adjusted as outlined in text. If bleeding continues after administering cryoprecipitates, platelet transfusion and heparin, a regimen of aminocaproic acid (Amicar) may be considered. Cryo-PPT = cryoprecipitate

Although there may be a transient excess prolongation of the prothrombin and partial thromboplastin times with the bolus, an "adequate" heparin effect will otherwise take several hours to achieve if no bolus is given. The heparin infusion should be adjusted to maintain the serum fibrinogen level above 100 mg per dl. If possible, this should be done without excessive prolongation of the PTT. Most patients will require escalation of the heparin dose towards "full" doses—that is, 15 to 20 units per kg per hour—as induction is initiated. This should be done as rapidly as possible with coagulation variables being measured at least every six hours initially.

Cryoprecipitate, which supplies predominantly fibrinogen and factor VIII, should be given before the heparin at a dose of 50 to 100 mg per kg if the initial serum fibrinogen level is less than 100 mg per dl and the patient is not bleeding significantly or less than 150 mg per dl if the patient is actively bleeding. Cryoprecipitate should continue to be given if heparin therapy alone does not maintain a fibrinogen level above 100 mg per dl. Platelet transfusions should be administered to maintain a platelet count of above 30,000 per μl. If a patient is actively bleeding, platelet counts should be maintained at greater than 50,000 per μl. An algorithm for the initial management of DIC is shown in Figure 3. In our experience, most patients will be adequately managed with heparin therapy without prolonging the PTT to more than 1.5 times the upper limit of the control range. In view of possible coexisting thrombocytopenia, extreme caution should be exercised when the PTT approaches this value as a result of giving heparin. Administration of cryoprecipitate and platelets may be required two to three times a day until the DIC comes under control.

For most cases, assaying the coagulation factors, such as factors V and VIII, is of little benefit. In addition, there is little role for the use of plasma as a source of factor replacement. Limited data suggest a possible therapeutic benefit from ϵ-aminocaproic acid.[20-22] Considering, however, the potential risk of thromboembolism associated with its use in cases of DIC, it must be used with caution in patients with APL.

Conclusions

In summary, although most patients with APL will have DIC, most can be successfully managed with the aggressive use of heparin plus platelet and cryoprecipitate transfusions as outlined above. The initial labeling index may help predict which patients are most likely to achieve a complete remission. Those patients who have a complete remission can be expected to have a survival comparable to responders with other AML subtypes. Finally, an anthracycline or amsacrine should be included as part of the induction chemotherapy regimen. Because marrow hypoplasia is not essential for complete remission, careful review is recommended before administering second or further courses of induction therapy.

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Acromegaly Update—Etiology, Diagnosis and Management

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Acromegaly is a disease with unique clinical manifestations. Its confirmatory diagnosis, however, requires basal and dynamic tests of growth hormone secretion. The measurement of circulating levels of somatomedin C has been a valuable addition to the diagnostic armamentarium. We review the etiology of acromegaly, with particular reference to the different histochemical and ultrastructural forms of somatotropic adenomas and their respective clinical behaviors. Ectopic sources of growth hormone-releasing hormone and of growth hormone itself are now well-recognized, though unusual, causes of acromegaly. The treatment of acromegaly is often problematic and far from uniformly successful. Initial enthusiasm for the results of surgical treatment has now been tempered by reports of increasing rates of recurrence on long-term follow-up. The roles of irradiation and pharmacotherapy are reviewed with particular emphasis on the use of bromocriptine, which has added a new dimension to the control of the somatic and metabolic manifestations of hypersomatotropism. Studies have been done recently using a long-acting somatostatin analog with encouraging results.

(Melmed S, Fagin JA: Acromegaly update—Etiology, diagnosis and management. West J Med 1987 Mar; 146:328-336)

Acromegaly, a syndrome of abnormal growth and proportion accompanied by metabolic derangements, was first described a century ago in 1886[1] by Marie and was the earliest pituitary disorder to be clinically recognized. Although autopsy studies documented the association of pituitary tumor with acromegaly,[2,3] not until 1909 did Bailey, Cushing and Davidoff confirm that anterior pituitary surgical intervention resulted in amelioration of some of the signs and symptoms of the disorder, thus further supporting the thesis that it was a syndrome of pituitary hyperfunction.[4] In a series of elegant animal experiments using injections of anterior pituitary extracts, Evans and Long[5] were able to produce features of gigantism in rats.

Physiology of Growth Hormone Secretion and Action

Growth hormone (Table 1) is a 191-amino acid polypeptide that is the predominant secretory product of the anterior pituitary.[6] Growth hormone secretion is under the dual control of hypothalamic stimulation and inhibition. Growth hormone-releasing hormone (GHRH) stimulates growth hormone secretion,[7,8] while somatostatin inhibits its secretion.[9] Peripheral hormones, such as estrogens, hydrocortisone and triiodothyronine, also appear to modulate the synthesis and secretion of pituitary growth hormone. Estrogens have been shown to enhance growth hormone secretion. Indeed, premenopausal women have greater growth hormone concentrations and secretory rates than normal men, whereas growth hormone levels in postmenopausal women are comparable to those in men.[10] Premenopausal women exhibit greater growth hormone responses to arginine than do men, but these responses in men can be made comparable to those of premenopausal women by pretreating with estrogens.[11] The implications of the increase in growth hormone secretion in women of reproductive age are attenuated by the fact that estrogens appear to inhibit production of somatomedin C.[12] Long- and short-term glucocorticoid excess results in suppression of growth hormone secretion,[10] which may play a role in determining the growth retardation of children with chronic glucocorticoid excess. Hypothyroid children have blunted growth hormone responses to insulin-induced hypoglycemia and GHRH,[13] and this may be relevant to the growth disturbance of thyroid hormone deficiency.

The growth-promoting effects of growth hormone are be-

TABLE 1.—*Nomenclature of the Hypothalamic-Pituitary Growth Hormone*

Hormone	*Source*	*Action*
Growth hormone-releasing hormone	Hypothalamus	Stimulates growth hormone secretion
Somatostatin	Hypothalamus	Inhibits growth hormone secretion
Growth hormone	Pituitary (somatotrope cell)	Stimulates somatomedin C; antagonizes insulin action
Somatomedin C	Liver; other tissues	Stimulates bone growth; stimulates cell replication

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CT = computed tomography
GHRH = growth hormone-releasing hormone
IGF-I = insulinlike growth factor I
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone

lieved to be mediated through the action of somatomedin C/insulinlike growth factor I (IGF-I).[14] Growth hormone stimulates the production of IGF-I in the liver, which is probably the major source of circulating IGF-I levels.[15] IGF-I, however, is also produced in most if not all other tissues, and such tissue production is responsive to growth hormone.[16] It is not clear whether the bioactivity of IGF-I is dependent on the circulating peptide (endocrine action) or if IGF-I is predominantly acting at or close to its site of synthesis on neighboring cells (paracrine action) or on the same cell that synthesized it (autocrine action). The complexity of these interactions is heightened by the fact that other somatomedins distinct from IGF-I and their binding proteins are also produced in various tissues, and they are variously regulated by growth hormone.[17] In addition, growth hormone has further direct peripheral actions in inhibiting the action of insulin on carbohydrate and lipid metabolism.[17-19] IGF-I has also recently been shown to act via a classic negative feedback loop in suppressing basal- and GHRH-stimulated gene expression and secretion of pituitary growth hormone.[20,21] IGF-I may also regulate hypothalamic somatostatin secretion.[20]

Etiology

The clinical features of acromegaly all result directly or indirectly from a sustained hypersecretion of growth hormone.[22] In recent years, the availability of specific hormone radioimmunoassays, computed tomographic (CT) scanning and sensitive immunohistologic techniques have resulted in the elucidation of several causes of acromegaly (Table 2).

Pituitary Causes of Acromegaly

The growth hormone-secreting cells (somatotropes) comprise about 50% of the cells of the anterior pituitary gland and are readily identified by sensitive and precise immunocytochemical and electron-microscopic techniques.[23] It is from these cells that growth hormone-secreting adenomas arise. The formation of a somatotropinoma (growth hormone-cell adenoma) probably accounts for more than 90% of the cases of acromegaly.[24] The pure growth hormone-secreting adenoma may either be densely granulated[25-38] with growth hormone-containing granules as seen on electron microscopy or sparsely granulated.[25,28,31,34,35,39-42] The former tumors contain large amounts of stored hormone and are usually slow growing, leading to an insidious clinical progression, often over many years. The sparsely granulated growth hormone-cell adenomas, however, are rapidly growing, locally invasive and often associated with suprasellar extension at clinical presentation. About 25% of all of these adenomas are bimorphous (combination of two cell types), which are classified as mixed growth hormone-cell and prolactin-cell adenomas.[41,43-48] About 10% of all somatotropinomas are derived from the acidophil stem cell.[26,49-51] These monomorphous (single cell type) growth hormone- and prolactin-containing tumors usually present with primary clinical features of hyperprolactinemia (galactorrhea, amenorrhea, impotence) and relatively mild acromegaly.

Mammosomatotropic monomorphous cell adenomas[52] are slowly growing growth hormone- and prolactin-containing benign tumors believed to be the mature variants of the acidophil stem cell adenomas. The patients clinically have acromegaly and high circulating growth hormone levels with normal to moderately raised prolactin levels.

Plurihormonal adenomas express growth hormone with prolactin, thyroid-stimulating hormone (TSH) or adrenocorticotropic hormone (ACTH).[28,53-55]

The natural history of acromegaly is highly variable, and the response of inappropriate growth hormone secretion to various stimuli and inhibitors in this condition is far from uniform. The ultimate relevance of this immunohistochemical classification would be enhanced if further correlations could be found between tumor cell types, dynamic growth hormone testing, such as to GHRH, thyrotropin-releasing hormone (TRH), dopamine agonists and glucose, and response to therapy, such as radiosensitivity or bromocriptine-responsiveness.

Most of the extrapituitary causes of acromegaly have only recently been fully documented and their pathogenesis clarified.

Aberrant somatotropic cell adenomas. These adenomas arise in pituitary tissue remnants in the sphenoid or parapharyngeal sinuses,[56-58] reflecting the embryologic origin of the anterior pituitary from Rathke's pouch.

Extrapituitary Causes of Acromegaly

Ectopic growth hormone-secreting tumors. The existence of extrapituitary growth hormone was suggested by the in vitro finding of immunoreactive growth hormone in lung adenocarcinoma,[59] breast cancer[60] and ovarian tissue extracts.[60] Recently a patient harboring a growth hormone-secreting intramesenteric islet cell tumor with acromegaly was cured after excision of the abdominal tumor, which was shown to express growth hormone messenger RNA.[61] Based on the features of this so-far-unique case, patients with ectopic growth hormone

TABLE 2.—*Etiology of Hypersomatotropism**

Pituitary
- Eutopic
  - Densely granulated growth hormone-cell adenoma
  - Sparsely granulated growth hormone-cell adenoma
  - Mixed growth hormone-cell and prolactin-cell adenoma
  - Mammosomatotrope-cell adenoma
  - Acidophil stem cell adenoma
  - Plurihormonal adenoma
- Ectopic
  - Aberrant growth hormone-cell adenoma
    - Sphenoid sinus
    - Parapharyngeal sinuses

Extrapituitary
- Ectopic growth hormone-secreting tumor
  - Pancreas
- Excess GHRH secretion
  - Eutopic—hypothalamic hamartoma
  - Ectopic—pancreatic islet cell tumors; bronchial and intestinal carcinoid
- Acromegaloidism

GHRH = growth hormone-releasing hormone

*Adopted from Melmed et al.[22]

secretion would be expected to have normal pituitary CT scans, no response of circulating growth hormone to TRH stimulation and undetectable levels of plasma GHRH.

Excess GHRH secretion: Eutopic: Hypothalamic hamartomas,[62] choristomas,[63] gliomas and gangliocytomas[64] may cause acromegaly. These tumors elaborate GHRH, causing acromegaly associated with excessive growth hormone secretion.

Ectopic GHRH secretion: Ectopic GHRH secretion has been documented in patients harboring pancreatic islet cell tumors[65-69] and lung and intestinal carcinoid tumors.[70-74] These patients present with the clinical features of classic acromegaly, accompanied by elevated circulating growth hormone and GHRH levels. Patients also often show mass effects (usually pulmonary) from their extrapituitary tumors, obvious metastatic disease or other humoral effects, such as insulin-induced hypoglycemia or carcinoid syndrome. The structure of GHRH was originally elucidated from extracts of pancreatic islet cell tumors removed from patients with this syndrome.[66,67,69] Following surgical removal of the tumors, growth hormone levels fell rapidly and clinical signs of acromegaly regressed. In some of these cases, examination of the pituitary showed evidence of growth hormone-cell (somatotrope) hyperplasia with a preserved reticulin network,[65,75] indicating the absence of an adenoma, wherein the reticulin network appears distorted.

The relative rarity of this condition was recently documented in a retrospective multicenter study of 177 unselected acromegalic patients where no cases of elevated circulating GHRH levels were found in previously undiagnosed cases.[76]

Acromegaloidism. Acromegaloidism, indistinguishable clinically from acromegaly, has been diagnosed in rare cases in patients with normal basal and dynamic growth hormone levels and no demonstrable pituitary or abdominal tumor. These patients may elaborate a unique growth factor distinct from growth hormone or somatomedin C.[77]

Clinical Features of Acromegaly

The classic physical features of acromegaly have intrigued physicians since the first description of the disorder (Table 3).

The clinical signs and symptoms of acromegaly are due to the effects of the local tumor mass in the pituitary, the peripheral effects of excessive growth hormone secretion and the endocrine effects of the disordered secretion of the other pituitary hormones.

Local Tumor Effects

In slow-growing tumors, the local features are usually not prominent. In the more aggressive tumors (usually seen in younger patients) these signs may be the presenting features.

Pituitary tumors enlarge and this may cause headache, visual field defects because of pressure on the optic chiasm or optic nerves or cranial nerve palsies.[78] Inferior expansion may erode into the sphenoid sinus. In rare cases these tumors may extend to the tips of the temporal lobe and may even cause uncinate seizures.[79] As the frequency of the early diagnosis of acromegaly increases, the prevalence of these local complications will decrease.

Patients with extrapituitary acromegaly will harbor either an abdominal or chest mass and may present with systemic features of carcinoid syndrome or even occasionally hypoglycemia from an islet cell tumor.

Effects of Excessive Growth Hormone Secretion

The earliest effects of excessive exposure to elevated growth hormone levels are coarsening of facial features with soft tissue swelling of the face, hands and feet.[80,81] This may occur insidiously, and the diagnosis is often confirmed by comparing serial photographs of patients taken over many years. Increased soft tissue volume results in patients noticing a progressively larger shoe size and ring diameter. These features depend both on the duration of the growth hormone hypersecretion and the degree of elevation of growth hormone levels. It appears that most of the somatic effects are mediated by excessive IGF-I levels,[16] whereas many of the metabolic effects, such as carbohydrate intolerance, are direct effects of growth hormone itself.[17-19] The prevalence of these clinical signs does not appear to differ substantially from the original description by Davidoff in 1926.[4]

As patients with acromegaly live longer, however, additional clinical features have become apparent. It appears that there is an association of colonic polyps in acromegalic patients who have skin tags.[82] Recently the association of colonic cancer and acromegaly has also been described, and this has confirmed the increased prevalence of cancer in cases of acromegaly.[82,83]

Other Endocrine and Metabolic Abnormalities

Acromegaly is associated with a multitude of metabolic abnormalities. The effects on carbohydrate and lipid metabo-

TABLE 3.—*Acromegaly—Clinical and Metabolic Features*

Local	
Visual field defects; cranial nerve palsy; headache	
Abdominal or chest mass	
Somatic	
Acral enlargement	Increased heel pad thickness; prognathism; hypertrophy of frontal bones; malocclusion; macroglossia
Musculoskeletal	Arthralgias; hypertrophic arthropathy; carpal tunnel syndrome; acroparesthesias; proximal myopathy
Skin	Hyperhydrosis; skin tags; acanthosis nigricans
Colon	Polyposis; carcinoma
Cardiovascular	Left ventricular hypertrophy; asymmetric septal hypertrophy; hypertension; congestive heart failure; arrhythmias; myocardial infarction
Sleep disturbances	Sleep apnea; narcolepsy
Visceromegaly	Salivary glands; liver; spleen; kidney
Metabolic and Endocrine	
Carbohydrate	Insulin resistance and hyperinsulinemia; impaired glucose tolerance; diabetes mellitus
Lipids	Hypertriglyceridemia
Mineral	Hypercalciuria; increased 1,25-dihydroxyvitamin D_3; increased urinary hydroxyproline
Electrolyte	Low renin; increased aldosterone
Gonadal	Menstrual abnormalities; galactorrhea; decreased libido; impotence; low testosterone-binding globulin
Thyroid	Thyromegaly; hyperthyroidism; low thyroid-binding globulin
Multiple endocrine neoplasia (I)	Hyperparathyroidism; pancreatic islet cell tumors

lism are probably due to a direct anti-insulin effect of growth hormone.[17-19] Curiously, despite hyperinsulinemia and clinically evident diabetes mellitus, the microvascular complications of diabetes seldom develop in persons with acromegaly. Reproductive disorders such as menstrual disturbances or galactorrhea in women and loss of libido and impotence in men are due to several factors, including associated hyperprolactinemia,[24,84] low testosterone-binding globulin levels and hypopituitarism with hypogonadotropinemia in patients with large pituitary tumors.[85] An increased prevalence of diffuse or nodular goiters is well recognized.[86] The interpretation of thyroid function tests may be complicated by a low thyroid-binding globulin level and an increased thyroid-binding prealbumin concentration.[86,87] ACTH and TSH deficiencies occur late in the natural history of the disease and require replacement therapy with hydrocortisone and thyroxine.

About 30% of patients with acromegaly have hyperprolactinemia. Elevated prolactin levels may be caused by a mixed somatotrope-lactotrope adenoma, production of growth hormone and prolactin from a single-cell-type tumor such as mammosomatotropic or acidophil stem cell tumor or, finally, by a plurihormonal adenoma consisting of two separate adenomas.[24] In larger, pure growth hormone-cell macroadenomas, pituitary stalk compression may also lead to hyperprolactinemia.

Hypercalcemia with abnormal calcium metabolism may occur in 3% to 16% of cases.[88] In a small proportion of these, this may be due to associated hyperparathyroidism as part of a syndrome of multiple endocrine adenomatosis (type I). In a review of 88 patients with this syndrome, 15 were found to have acromegaly.[89] Hypercalciuria is seen more commonly. In this regard, increased concentrations of 1,25-dihydroxyvitamin D_3 have been reported in patients with acromegaly, and these have been shown to decrease after treatment.[88] Increased 1,25-dihydroxyvitamin D_3 levels may play a role in the hypercalcemia and increased bone turnover occasionally encountered in this disease.[90]

Diagnosis of Acromegaly

The clinical diagnosis of acromegaly is usually clear-cut in long-standing cases, but may be subtle in the early stages of the disease. The diagnosis of acromegaly is based on strict biochemical criteria. Upper levels of normal for serum growth hormone in adults are 5 ng per ml in male patients and 10 ng per ml in female patients. The basal levels of growth hormone fluctuate physiologically,[91] however, and elevated levels are also found in patients who are stressed and in those with chronic renal failure, poorly controlled diabetes mellitus, malnutrition, anorexia nervosa and cirrhosis.[92] The finding of a single elevated serum growth hormone level is therefore not diagnostic of acromegaly. The absence of suppression of serum growth hormone levels (< 5 ng per ml in male patients and < 10 ng per ml in female patients) two hours after an oral glucose load (75 grams) establishes the diagnosis of pathologic hypersecretion of growth hormone in more than 90% of cases. About 20% of patients with acromegaly will in fact have a paradoxic elevation of growth hormone levels two hours after oral administration of glucose.[93-96] A stimulation of already elevated growth hormone levels after thyrotropin-releasing hormone administration is seen in about 75% of cases.[97] Clearly, therefore, a few patients with acromegaly, while manifesting the features of growth hormone excess, may have normal fasting growth hormone levels, normal growth hormone suppression after an oral glucose tolerance test and no stimulation of growth hormone after TRH administration.

The growth hormone dependency of IGF-I and its long half-life—in virtue of its almost complete binding to specific carrier proteins[98,99]—has aroused great interest in its value as a tool for diagnosis and follow-up of acromegaly. Several studies have pointed out that IGF-I levels appear to correlate better than fasting growth hormone levels or those after a one-hour glucose load with activity of the disease, such as heel-pad thickness.[100,101] IGF-I levels thus appear to represent a readily measurable assessment of growth hormone bioactivity. IGF-I levels can also increase in a number of physiologic conditions, such as puberty and late pregnancy,[102] and may be extremely low in persons with malnutrition.[103] The overlap, however, between normal persons and those with active acromegaly is small. Measuring IGF-I levels is appropriate as part of the initial diagnostic workup and the monitoring of the response to therapy in acromegaly. Several groups, however, have contended that neither growth hormone nor IGF-I levels alone correlate well with clinical responses following treatment of acromegaly.[104,105] Thus, somatomedin assays should supplement basal and dynamic tests for growth hormone for the endocrine diagnosis and follow-up of somatotropic adenomas.

Additional anterior pituitary function testing that provides useful information for postsurgical management includes measuring serum prolactin levels, doing thyroid function tests and assessing ACTH reserve.

Although plain lateral skull x-ray films reveal abnormalities of the sellar contour in 80% to 90% of cases,[106] the presence of microadenomas (less than 10 mm) is not detected by this method. High-resolution CT scanning is the best imaging technique currently available for the study of pituitary adenomas. While macroadenomas are often visualized as hyperlucent areas, microadenomas of up to 5 mm can be seen as hypodense or isodense intrapituitary lesions.[107] CT scanning has been disappointing in the study of the sellar anatomy following a pituitary operation or irradiation.[107] Suprasellar extension of adenomas or the presence of an empty sella, however, can be reliably detected by CT. Nuclear magnetic resonance imaging techniques have recently been introduced and show great promise. They show with precision the effects of the pituitary tumor mass on adjacent structures, particularly the visual pathway, and are better able to distinguish the intrasellar cerebrospinal fluid cistern of the "empty" sella from other lesions that present with a hypodense CT appearance such as fibrous, necrotic or cystic tissue.[108] There may still be an occasional role for angiographic techniques in persons harboring large pituitary masses in whom the relationship of the tumor to the neighboring blood vessels must be defined.[106]

The search for an extrapituitary cause of acromegaly through abdominal and chest CT scanning before therapy directed at the pituitary is probably not cost-effective when done on a routine basis as these are relatively rare conditions.[76] If there are symptoms pointing to an extrapituitary tumor, carcinoid syndrome or hyperinsulinemia; a normal pituitary CT scan with no response of growth hormone to TRH administration, or increased GHRH levels are encountered, then a CT search for an ectopic source of growth hormone or GHRH is indicated.

Therapy for Acromegaly

The aims of therapy for acromegaly are as follows:

- To treat the pituitary lesion, thus correcting or preventing local complications.
- To totally suppress disordered pituitary secretion of growth hormone, thus preventing progression of physical disfigurement and the metabolic or systemic effects of hypersomatotropinemia.
- To prevent or rectify other pituitary tropic hormone disorders.

Table 4 summarizes the criteria for the cure of acromegaly that have been used by several groups in recently published series. As will be discussed below, no single therapeutic option (Table 5) really offers a 100% successful cure of acromegaly. Medical or radiation therapy will often be required as adjuvants to surgical treatment. The development of newer pharmacological agents, especially somatostatin analogs, certainly holds much future promise.

Radiation Therapy

Conventional radiation therapy is used both as a primary and an adjuvant form of therapy in acromegaly.[114,115]

A total dose of 5,000 rads is administered over four to six weeks. The time required for this to effectively lower growth hormone levels by 50% is usually at least two years. The longer the time interval after irradiation, the greater the effectiveness of the treatment.[85,115-117] After ten years, normal growth hormone levels are seen in about 75% of persons with acromegaly. The arrest of tumor growth is almost uniformly seen, and most growth hormone-cell adenomas do shrink after irradiation.

Side effects. Radiation damage to the surrounding tissues may occur, especially if more than 5,000 rads are administered.[115-117] Hypopituitarism will develop in about 50% of patients after ten years. Hypocortisolism and hypogonadism are the usual tropic hormone deficits, while isolated hypothyroidism occurs in only about 10% of these patients. Mixed hypocortisolism and hypogonadism will develop in about 5% of patients.[115-117]

Proton beam therapy has also been used with considerable success in the treatment of acromegaly.[118] The advantage of this form of irradiation is that a patient can receive the total radiation dosage (4,500 to 6,500 rads) in only one or two visits without causing skin damage.

The slowness of the response seen with radiation therapy usually makes it an inappropriate option for young patients who may be alarmed by the prospect of progressive physical deformities. Furthermore, glucose intolerance and hypertension may be serious complications of acromegaly and clearly a rapid fall in circulating growth hormone levels would be desirable to prevent development or exacerbation of these complications.

TABLE 4.—*Criteria for Absolute Cure of Acromegaly*

Fasting AM growth hormone levels are less than 5 ng/ml in male patients and less than 10 ng/ml in female patients
Growth hormone secretion is suppressible after an oral glucose tolerance test*
Normal circadian rhythm of growth hormone secretion reappears†
Growth hormone levels increase normally after provocative stimulation‡§‖¶
IGF-I levels are normal#
Paradoxic growth hormone responses disappear†§‖

IGF-I = insulinlike growth factor I

*From Ouabbe[109]
†From Jaquet et al.[110]
‡From Faglia et al.[95]
§From Arafah et al.[111]
‖From Hoyte and Martin.[112]
¶From Pearson et al.[113]
#From Clemmons et al.[100]

TABLE 5.—*Treatment Options in Acromegaly*

Surgical
Transsphenoidal pituitary adenomectomy
Primary extrapituitary tumor resection
Radiation
Conventional supervoltage
Proton beam
Medical
Dopaminergic agonists (bromocriptine; pergolide mesylate)
Somatostatin analogs

Surgical Management—Transsphenoidal Surgery

The earliest cures of acromegaly were in fact described by Cushing in 1909, who used the transsphenoidal approach to surgically remove pituitary tumors.[119] Today, the most frequently used form of therapy in acromegaly is transsphenoidal pituitary adenomectomy done by a skilled and experienced neurosurgeon. A transfrontal pituitary operation is reserved for patients harboring large tumors with significant suprasellar extension or contiguity with blood vessels or optic nerves.[120,121]

The results of selectively resecting a growth hormone-cell adenoma are clear-cut and rapid. Growth hormone levels fall to normal within an hour of tumor excision, and the soft tissue and metabolic effects of elevated growth hormone levels are ameliorated almost immediately. The hard tissue changes induced by the acromegaly are, however, irreversible.

The following clinical and biochemical features will predict the success of surgical treatment[122,123]:

- Microadenoma is totally confined within the pituitary fossa.
- Random serum growth hormone levels are less than 40 ng per ml.

Patients fulfilling these two criteria will have an initial success rate of almost 90% as assessed by a reduction in serum growth hormone levels to less than 5 ng per ml.[122-126] Normal pituitary function is usually restored postoperatively if the tumor is well encapsulated. Despite these good results observed in most major centers, recent evidence has indicated that long-term results (five years and later) in these patients are not at all as favorable.[127] Tumor recurrence with or without clinical features of acromegaly and evidence of failure to suppress growth hormone levels after oral administration of glucose have been observed in patients who had initially been "cured." Further data from follow-up studies are required to allow a fuller evaluation of the long-term results of the transsphenoidal pituitary operation.

Side effects. Clearly the most important endocrine side effect of surgical treatment is damage to the remainder of the pituitary gland with resultant pituitary failure and the necessity for life-long hormone replacement.[95,109]

Surgical morbidity including cerebrospinal fluid leaks, sinusitis, central nervous system damage, hemorrhage, transient or permanent (infrequent) diabetes insipidus and bacte-

rial or sterile meningitis occurs in about 5% of all patients. An empty sella syndrome postoperatively may in rare cases lead to visual impairment. The incidence of these complications depends on the size of the tumor.[122,123,125,126]

Finally, as with any major operation, about a 1% mortality rate exists. These operative deaths are usually only seen in patients with large invasive tumors.[121]

It should be emphasized that the recurrence of acromegaly after surgical treatment may indicate incomplete surgical resection of tumor tissue.[122] Although growth hormone-cell adenomas are usually well confined, functioning tumor cells may invade the dura and are thus difficult to visualize and resect.

Medical Treatment of Acromegaly

Bromocriptine. 2-Bromo-α-ergocriptine, a lysergic acid ergot derivative, has recently been approved by the Food and Drug Administration for use in the treatment of acromegaly. This dopamine agonist binds to pituitary dopamine receptors and will cause a substantial suppression of prolactin secretion in normal patients and those with prolactin-secreting adenomas. Because neoplastic somatotropes probably respond inappropriately to dopamine agonists by suppressing growth hormone secretion in more than 50% of persons with acromegaly,[128] bromocriptine is used as both a primary and an adjuvant medication for acromegaly.

The doses of bromocriptine used in acromegaly are usually higher than those required to suppress prolactin secretion. It is noteworthy, however, that if a beneficial effect of the use of bromocriptine is to be observed, it is usually seen with doses of as much as 20 mg bromocriptine a day.[129-132] Higher doses are usually unwarranted, as side effects of the drug will become more apparent. These include headache, nasal stuffiness, nausea, vomiting, transient postural hypotension, cold-induced peripheral vasospasm, depression, nightmares and hallucinations.[133] These side effects are usually reversible after decreasing the dose.

In more than 20 published series from Western Europe and the United States, it appears that basal serum growth hormone levels are decreased to less than 10 ng per ml in about 50% of cases (range 10% to 80%). A growth hormone level of less than 5 ng per ml has been found in 20% of reported cases (range 5% to 60%),[85] while shrinkage of tumor size probably only occurs in about 10% to 20% of cases in published series.[134,135] Interestingly, however, most patients (about 70%) noted a significant improvement in clinical well-being, including reduction of perspiration, decreased soft tissue swelling and decreased ring size.[136] There is controversy regarding the correlations between clinical responses to bromocriptine therapy and serum levels of growth hormone after oral glucose is given and IGF-I levels are measured. While some authors claim that growth hormone levels are a more faithful index of therapeutic response,[104,136,137] others[105] have found that IGF-I levels are superior in this respect. In fact, Wass and co-workers have described a subgroup with unchanged growth hormone levels but decreased IGF-I levels who had improved clinically and metabolically.[105] Thus it appears that bromocriptine may induce clinical improvement in many patients in spite of persistently raised growth hormone or IGF-I levels (or both). Some groups have reported that bromocriptine may selectively suppress the monomeric, biologically active form of growth hormone,[138] whereas immunoreactive growth hormone levels remain unchanged or only slightly decreased. Hizuka and associates and others, however, have found no differences in elution profiles of growth hormone on Sephadex G 100 chromatography or alterations in growth hormone-binding properties in patients receiving bromocriptine.[139,140] In addition, an increased clearance of biologically active growth hormone has been reported,[138] possibly due to increased blood flow to liver and kidneys, sites of growth hormone metabolism. Thus, it is tempting to conclude that bromocriptine may indeed have a beneficial peripheral effect by impairing growth hormone bioactivity, unrelated to its direct effect on somatotropes. Further studies are required to clarify this possibility.

Predicting response to bromocriptine therapy. It has recently been shown that an initial suppression of growth hormone levels by 50% in response to the administration of 2.5 mg bromocriptine will reliably predict the long-term positive response to bromocriptine therapy. Furthermore, it would appear that TRH stimulation of growth hormone levels may predict a concordant suppressive effect of growth hormone by dopamine agonist therapy.[141] The presence of significant hyperprolactinemia has also been suggested as a positive predictor of growth hormone response to bromocriptine.[142]

Further studies are necessary to confirm the validity of these predictive tests.

Somatostatin analog. Because somatostatin is a physiologic inhibitor of growth hormone secretion, it was a natural candidate as a pharmacologic tool in treating acromegaly. Recently an octapeptide somatostatin analog—SMS 201-995, D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr (OH)—with high potency and prolonged inhibition of growth hormone secretion has been developed.[143] This analog, administered subcutaneously, has been successfully used to lower growth hormone levels in acromegaly. Indeed, SMS 201-995 has recently been found to provoke a prolonged decrease of growth hormone levels in seven of eight acromegalic patients tested. A short-lived suppression of insulin levels, however, with a concomitant rise in blood glucose levels was also noted.[144-146] Clinical trials currently under way will no doubt further evaluate the safety and efficacy of this promising new form of therapy.

Other medical treatments. Estrogens,[147] progesterone,[148] chlorpromazine[149] and cyproheptadine hydrochloride[150] have been used with varying degrees of success in the treatment of acromegaly.

Conclusion

Although recent studies have led to major advances in our understanding of the pathophysiology and etiology of acromegaly, successful therapy still remains elusive for many patients. The initial success of the transsphenoidal operation has been followed by less enthusiastic reports of long-term disease recurrence. Medical treatment, either primary or adjunctive, is likely to play an increasingly important therapeutic role during the next few years.

The significant progress made in unraveling the complexities of acromegaly in the past 100 years illustrates the fruitful application of advances in neuroendocrine physiology and cellular biochemistry to the understanding of this heterogeneous clinical disorder.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Gastric Balloon for the Treatment of Obesity

QUESTION:

Is the gastric balloon, a soft, plastic inflatable device placed endoscopically in the stomach in order to control appetite, considered accepted medical practice to aid weight reduction in obese patients?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery and Internal Medicine, use of the gastric balloon for the treatment of obesity should be considered investigational until controlled clinical studies, some of which are now in progress, define the full extent of potential complications and document its safety and long-term effectiveness in maintaining weight loss. The gastric balloon is a soft, plastic device that is placed in a patient's stomach endoscopically. After inflation, it is left to float free in the upper stomach for several months. The balloon is intended to be a temporary treatment, used with diet therapy and behavior modification for those obese patients who have failed to lose weight with these conventional methods alone.

In the short term, the gastric balloon has been shown to curb appetite and aid in weight reduction, with a minimum of serious complications. In fact, the Food and Drug Administration has approved one device based on this evidence. However, the advisory panels consider widespread use of the gastric balloon premature, until more clinical data are accumulated and the long-term results of weight maintenance following removal of the balloon are clearly established.

Medical Progress

The Role of Immunotherapy in Type I Diabetes Mellitus

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Type I diabetes mellitus appears to result from an insidious immunologic destruction of pancreatic β-cells in genetically susceptible persons exposed to one or a series of environmental insults. This genetic susceptibility is related to alleles located on the sixth chromosome in the HLA-DR or an adjacent region. With superimposition of a viral or other environmental triggering event, cell- and antibody-mediated events are activated that lead to the specific autorejection of β-cells and consequent insulin deficiency. Immunosuppressive strategies to impede or halt complete destruction of β-cells, using cyclosporine, have already been initiated in both animals and humans with diabetes mellitus. Because of the potential toxicity of all current immunosuppressive regimens, such therapies cannot, at this time, be considered for wide-scale use in persons with type I diabetes. Reported inductions, however, of insulin independence in patients with newly diagnosed type I diabetes using cyclosporine or other agents underscore the role of the immune system in the pathogenesis of the disease and highlight the need to develop safer, more specific immunomodulation designed to avoid complete β-cell destruction.

(Geffner ME, Lippe BM: The role of immunotherapy in Type I diabetes mellitus [Medical Progress]. West J Med 1987 Mar; 146:337-343)

Over the past ten years, three important factors have been identified that appear to be fundamental to the development of type I diabetes mellitus in humans: genetic, environmental and immunologic. To date, type I diabetes mellitus has been treated with insulin and other supportive measures; therapies have not generally been directed toward the basic cause of the condition. Other disorders also associated with immunologic dysregulation, including rheumatoid arthritis, multiple sclerosis and glomerulonephritis, are now being treated with experimental immunotherapy regimens, and some similar protocols are now being applied to persons with diabetes mellitus of new onset.[1] In this review, we present the current theories of the pathogenesis of type I diabetes mellitus and prospects and strategies for immunotherapeutic intervention.

Genetic Susceptibility

The strongest evidence for genetic factors contributing to type I diabetes mellitus is its relationship to the human leukocyte antigen (HLA) system. While different from analyses that use statistical occurrence in classical Mendelian genetics, a linkage association between the HLA antigens DR3 and DR4 can be found in more than 95% of children with type I diabetes.[2,3] These same alleles, however, are also present in 40% of nondiabetic whites in control populations. The HLA-DR molecules, along with the recently described DP and DQ molecules, are the class II transplantation antigens of the major histocompatibility complex coded for in the HLA-D region of the sixth chromosome and normally expressed as heterodimeric glycoproteins on the surface of immune-competent cells. Using molecular biologic cloning techniques to examine differences in restriction fragment length polymorphisms generated by cutting of DNA with specific enzymes, Owerbach and co-workers reported that a specific 3.7-kilobase (kb) segment of DNA frequently found in nondiabetic persons with HLA-DR4 or -DR3/4 (30% to 40%) was rarely found in diabetic patients with the same HLA-DR types (0% to 2%). Instead, an 18-kb fragment was found frequently in persons with diabetes with HLA-DR4 and -DR3/4 but not in nondiabetic controls who were DR-matched.[4] Further studies suggest that the molecular defect may reside not in the HLA-DR locus, but nearby at the HLA-DQ β-chain gene or in neighboring intervening sequences (introns).[5] That identical twins show only a 25% to 30% concordance rate for type I diabetes[6,7] suggests that additional factors, presumably environmental in origin, are necessary for expression of the disease.

Environmental Factors

The importance of a role for an antecedent viral infection as the environmental triggering mechanism is suggested by similarities to the animal disease induced by the encephalomyocarditis virus, Mengo virus, and Coxsackie B4 virus[8]; when Coxsackie B4 virus from the pancreas of a child who died at diagnosis of ketoacidosis was inoculated into mice, it produced hyperglycemia,[9] and an increased incidence of diabetes following mumps[10] and congenital rubella infections.[11] About 85% of cases of type I diabetes occur between August and April, with the peak incidence during the winter months.[10] Such seasonality is probably related to final β-cell demise that long after the initiation of the original insult leads to presentation with overt symptoms of diabetes. Viruses may initiate autoimmune destruction (see below) because of shared antigenic determinants with β-cells, inducing neoantigen expression by β-cells or by directly attacking β-cells.

Other nonviral environmental agents have been linked to β-cell damage. Insulinopenia has followed human exposure to

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ABBREVIATIONS USED IN TEXT

HLA = human leukocyte antigen
ICCA = islet-cell cytoplasmic antibodies
ICSA = islet-cell surface antibodies
NOD = nonobese diabetic

the rodenticide Vacor (containing *N*-3-pyridylmethyl-*N'*-p-nitropheryl urea), and epidemiologic evidence has implicated the consumption of cured or smoked mutton (containing *N*-nitrosamine compounds) to the onset of type I diabetes mellitus in Icelandic boys.[12]

Immunologic Defects

Antibody-Mediated Causes

The co-occurrence of type I diabetes mellitus with other autoimmune endocrine diseases, including Hashimoto's thyroiditis, Graves' disease, Addison's disease and pernicious anemia, suggests that abnormal immunologic surveillance against self is involved in its pathogenesis (Table 1).[13]

A role for humoral factors in the pathogenesis of type I diabetes mellitus is based on the detection of circulating antibodies against islet-cell components in as many as 85% of children at the time of diagnosis.[14] Two major types of islet-cell antibodies have been identified: cytoplasmic and surface. Attempts to standardize the methods for determining islet-cell cytoplasmic antibodies (ICCA) using indirect immunofluorescence and frozen-section specimens of blood group O human pancreas are in progress.[15] While ICCA are not mounted specifically against β-cells, the reaction clearly includes β-cells.[16] The exact antigen(s) to which the islet-cell antibodies are directed is(are) unknown, but appears to include a 64-kilodalton surface membrane component specific for β-cells.[17] That the islet-cell cytoplasmic autoantigen has properties of a sialic acid-containing glycolipid is suggested by the studies of Nayak and associates.[18] The exact role of these antibodies in the pathogenesis of type I diabetes remains unknown. ICCA may, however, be a marker for, rather than the cause of, β-cell destruction stimulated by intracytoplasmic antigens (previously unrecognized or altered by the triggering events leading to type I diabetes). On the other hand, islet-cell surface antibodies (ICSA) are cytotoxic to β-cells in vitro in the presence of complement.[13,19-21] Such antibodies have been found in 35% of persons with type I diabetes mellitus with an increased frequency within two years of diagnosis.[22]

The importance of humoral factors in the cause of type I diabetes is also suggested by the work of Kanatsuna and colleagues, who found that glucose-stimulated insulin release from perifused dispersed islets is inhibited using immunoglobulin-enriched preparations of serum from patients with type I diabetes.[23] Additionally, serum from patients with type I diabetes showed cytotoxicity in isolated hamster pancreatic islets in the presence of guinea pig complement.[24] Maruyama and co-workers have suggested that ICSA-containing serum is cytotoxic to human pancreatic β-cells only if cloned in the presence of healthy human lymphocytes.[25] Thus, it is unclear whether such in vitro studies of humorally mediated cytotoxicity reflect the in vivo situation.

ICCA have been found as much as eight years before the onset of clinically unmistakable diabetes in high-risk siblings observed in a prospective fashion.[26] The natural history of immunologic and metabolic defects during this latency period is just beginning to be characterized. In the Barts-Windsor Prospective Family Study in which first-degree relatives of patients with type I diabetes mellitus in England have been followed since 1978, ICCA have developed in 54 relatives in 160 families. Of these, six have gone on to have diabetes associated with ICCA (immunoglobulin G) in all cases.[27] Such ICCA, of the complement-fixing variety, may occur transiently over a five-year period, as has been recently shown by Spencer and associates in 12 of 20 initially positive first-degree relatives of children with type I diabetes.[28] Millward and co-workers have also reported ICCA to be transiently present.[29]

TABLE 1.—*Immunologic Defects in Type I Diabetes Mellitus*

Antibody-Mediated
Islet-cell cytoplasmic antibodies*
Islet-cell surface antibodies*
Anti-insulin antibodies*
Association with other diseases associated with organ-specific antibodies*
Cell-Mediated
Insulitis†
Decreased percentage of suppressor/cytotoxic T lymphocytes*
Activated T cells (Ia-antigen-bearing)*

*Also noted in the prediabetic state
†Presumably present in the prediabetic state.

Srikanta and colleagues at the Joslin Clinic (Boston) measured ICCA in 1,723 parents, siblings and offspring of patients with type I diabetes. Initial screening detected a prevalence of ICCA of 0.9% (16/1,723). During a maximal observation period of two years, type I diabetes developed in 2 of the 16 first-degree relatives positive for ICCA but in only 1 of 1,707 subjects without detectable ICCA.[30] Similarly, Ginsberg-Fellner and co-workers reported, from a group of 351 siblings to propositi with type I diabetes observed for an average of 54 months, progression to overt diabetes in 10. Eight of the ten were HLA-identical to their diabetic probands, and ICCA and ICSA were detected from 2 to 74 months before diagnosis in 9/10 and 10/10 subjects, respectively.[31]

The recently described finding of anti-insulin antibodies in as many as 40% of previously untreated patients with newly diagnosed type I diabetes indicates that they may be another marker of immunologic β-cell damage.[32-35] Anti-insulin antibodies, like islet-cell cytoplasmic and surface antibodies, have also been found in the serum of members of high-risk populations before diabetes eventually developed—that is, close relatives of probands affected with type I diabetes[36] and some young persons with asymptomatic or transient glycosuria or hyperglycemia.[36]

Cell-Mediated Causes

Supporting a role for cell-mediated immunologic participation in the pathogenesis of type I diabetes mellitus[37,38] is the finding of lymphocyte and macrophage (mononuclear cell) infiltration (insulitis) in the islets of some persons with newly diagnosed disease.[39] The specificity of the destructive process against β-cell components of the islets is shown by preservation of a normal mass of α (glucagon), δ (somatostatin) and pancreatic polypeptide cells.[40] The potency of the autoimmune response that leads to β-cell destruction is emphasized by the rapid appearance of insulitis (without exocrine involvement) and loss of graft function in three persons with diabetes

who received pancreas transplants from their identical nondiabetic twins without concurrent immunosuppression.[41]

Disturbances of cell-mediated immunity in type I diabetes were suggested by the early work of Nerup and associates who showed the presence of antipancreatic cellular hypersensitivity using the leukocyte migration test.[42,43] MacCuish and colleagues have shown significant lymphocyte blastogenic transformation in these patients when their lymphocytes were cultured with the β-chain of bovine insulin.[44] These investigators also found positive lymphocyte blastogenesis in a few patients before the onset of diabetes.[44,45] Maclaren and Huang have reported increased specific cytoadherence to and cytotoxicity of dispersed cultured human insulinoma cells.[46]

Varying results have been reported concerning the relative percentages of lymphocyte subclasses in type I diabetes mellitus, including elevated numbers of B lymphocytes,[47] decreased T lymphocytes and no alterations of either B or T lymphocytes.[48] More recently, several investigators have reported exaggerated antibody-dependent cell-mediated cytotoxicity in the form of excess E rosette-forming lymphocytes of low affinity (killer [K] cells) in more than 50% of persons with newly diagnosed diabetes mellitus and also in some ICCA-positive nondiabetic siblings.[49-51] These K cells, which constitute one type of lymphocyte along with T and B cells, are felt to be involved in tissue-damaging events associated with allograft rejection, immune modulation and the elimination of virus-infected cells.[52] They may also be involved in the pathogenesis of organ-specific autoimmune endocrinopathy.[53] Additionally, increased numbers of circulating Ia-antigen-bearing T cells have been reported in persons with newly diagnosed type I diabetes, but not in those with long-standing disease, type II diabetes or in normal controls.[54] Normally the Ia antigen, which is coded by the HLA-D region of the sixth chromosome, is present on all B lymphocytes and monocytes, with expression of small quantities on some normal circulating T cells. Because normal T cells when challenged in vitro by mitogens may acquire the Ia antigen, its presence in persons with the recent onset of diabetes suggests activation of the immune system. Activation of T lymphocytes in patients with type I diabetes is further suggested by the expression of the so-called Tac antigen in 6.2% of mononuclear cells from patients whose duration of disease is less than two years compared with only 2% of these cells in patients whose duration is greater than or equal to three years or in controls.[55] Similar findings have also been reported using a monoclonal anti-Ia antibody.[56]

Using monoclonal antibodies, the percentage of suppressor/cytotoxic T cells (OKT 8) has been shown to be low and the percentage of helper/inducer T cells (OKT 4) high at the time of diagnosis.[57,58] In another study using monoclonal antibodies, the number of suppressor T lymphocytes was decreased at diagnosis while that of cytotoxic T lymphocytes was normal.[59] Six of seven newly diagnosed patients in the study of Pozzilli and co-workers had evidence of activated T cells (4F2 and 5E9). Analysis of lymphocyte subtypes in type I diabetes, measuring tritium-labeled thymidine incorporation into concanavalin A-stimulated normal donor lymphocytes, has shown diminished suppressor cell activity in persons with newly diagnosed diabetes[60,61] and also in some with disease of longer duration.[62,63] Other cell-mediated immune defects in type I diabetes mellitus that have recently been reported include the in vitro suppression of insulin release following incubation with lymphocytes from persons with type I diabetes[64] and, specifically, with T-lymphocyte-enriched subsets (OKT 3^+).[65] Migration of purified peripheral T lymphocytes from subjects with type I diabetes was inhibited in response to human pancreatic antigens obtained from insulinoma or β-cell hyperplasia tissue obtained at a surgical procedure.[66]

TABLE 2.—*Contrast Between Diabetes Mellitus in Humans and in BB Rats*

Similarities
Major histocompatibility complex association
Morphologic findings of insulitis
Islet-cell surface antibodies
Other tissue-specific antibodies
Prevention and modification by immune interventions
Immunosuppression (thymectomy, antilymphocyte serum, irradiation)
Reconstitution (neonatal bone marrow transplant, circulating leukocytes)
Differences
Profound lymphopenia (mostly T cell) precedes insulitis
Abnormal lymphocyte function (decreased in vitro mitogenicity)

Activation of the immune system in patients with type I diabetes mellitus appears to involve the presentation of the islet (β-cell) autoantigen to helper T lymphocytes bearing specific receptors for the autoantigen. Recognition of the autoantigen is contingent on simultaneous recognition of class II (HLA-DR) antigens similar to those normally present on the T-helper cell. Class II antigens are not normally expressed by islet cells, but have been found on some β-cells and in high density on pancreatic capillary endothelium from a 12-year-old girl who died within 24 hours of a diagnosis of type I diabetes mellitus.[67,68] Once activated, the T-helper cell, governed by the laws of antigen restriction, can direct cytotoxic T or B lymphocytes or both. γ-Interferon production has also been increased in a significant number of persons with newly diagnosed disease, consistent with the presence of activated T cells and a cell-mediated response against β-cells.[69] Using cultured human islet cells from adult and fetal pancreases and from an insulinoma, γ-interferon has been shown to increase in vitro expression of class I (HLA-A, -B and -C) antigens, but not class II (DR) antigens. This upregulation of HLA-A, -B and -C proteins on β-cells by γ-interferon may account for increased targeting of cytotoxic T lymphocytes to β-cell autoantigens.[70]

Animal Models of Type I Diabetes

The contribution of aberrant immunologic function to the development of insulin dependence is also supported by the results of investigations of diabetes mellitus in animal models, including the "BB" (Bio Breeding Laboratories) Wistar rat and the nonobese diabetic (NOD) mouse.[71,72] BB rats are nonobese and, in about 50% of offspring (both male and female), hyperglycemia, hyperglucagonemia, ketosis and insulitis develop at between 60 and 180 days of age. BB rats (Table 2) differ immunologically from humans with type I diabetes because these animals appear to have a severe underlying quantitative and qualitative T-cell immunodeficiency.[73] Similarities to the human disease, albeit in a "telescoped" form, with complete β-cell destruction within one to three weeks in the rats, include histologic evidence of insulitis; apparent coding in the rat HLA equivalent; the development of islet-cell surface antibodies (before the onset of glycosuria)

TABLE 3.—*Experimental Immunotherapies in Human Type I Diabetes Mellitus*

Agent(s)	*Year*	*Reference Source*
Levamisole hydrochloride	1980	Cobb et al, 1980[84]
Plasmapheresis alone or with azathioprine, antilymphocyte globulin and prednisone	1980, 1983	Ludvigsson et al, 1983[85]; Leslie and Pyke, 1980[86]
Interferon	1981	Rand, et al, 1981[83]
Glucocorticoids	1981, 1982	Elliot et al, 1981[80]; Elliot et al, 1981[81]; Jackson et al, 1982[82]
Antithymocyte globulin and prednisone	1983	Silverstein et al, 1983[87]
Cyclosporine	1984-1986	Stiller et al, 1984[93]; Assan et al, 1984[94]; Mandrup-Poulsen et al, 1985[95]; Stiller et al, 1985[96]; Feutren et al, 1986[97]
Antiblast monoclonal antibody C3L 1	1985	Culler et al, 1985[88]
Gamma globulin	1985	Heinze et al, 1985[89]
Azathioprine alone or in combination with prednisone or methylprednisolone sodium succinate (or both)	1985, 1986	Harrison et al, 1985[98]; Silverstein et al, 1986[99]

that recognize a 64-kilodalton β-cell membrane component[74]; the frequent co-occurrence of lymphocytic thyroiditis, and the development of antibodies to thyroid, gastric parietal cell and smooth muscle tissues. In BB rats, a pathogenetic role for cell-mediated immunity is supported by the finding that diabetes with insulitis could be induced by the passive transfer of spleen cells alone or in combination with lymph node cells from affected animals.[75] When "immunologically reconstituted" by transplantation of neonatal bone marrow from another strain of rat or by weekly transfusions of whole blood from a nondiabetic strain of BB rats, diabetes was prevented in susceptible BB rats, suggesting correction of an underlying immunodeficiency state.[76,77] Immunosuppressive therapies, including antithymocyte globulin, total lymphoid irradiation, neonatal thymectomy and administration of cyclosporine, have been shown to prevent diabetes in susceptible BB rats. Specifically, of 40 such BB rats treated with cyclosporine, none became diabetic and all had histologically normal pancreases compared with 40 untreated animals, 30 of which became diabetic.[71]

Insulitis with lymphocytic infiltration develops in another animal model of type I diabetes mellitus, the NOD mouse,[72] in greater than 90% of both males and females, by the age of 200 days. Although clinical symptoms, including ketosis, are much more common in female mice, insulitis and overt diabetes can be prevented by allogeneic bone marrow transplantation.[78] Diabetes can also be prevented in the mouse with low-dose streptozocin-induced diabetes using antilymphocyte serum and, in some species, with the administration of azathioprine and inosiplex (Isoprinosine).[79]

Immunotherapy in Human Diabetes

Based on the evidence that immunologic dysregulation is present at the time type I diabetes mellitus is diagnosed and on the successes of immunotherapy in diabetic animals, several clinical trials have been undertaken in both children and adults to determine if immunotherapy can modify the course of diabetes mellitus of recent onset in humans (Table 3). Initial regimens, tested for as long as a year, included glucocorticoids[80-82]; human leukocyte interferon[83]; levamisole hydrochloride[84]; plasmapheresis alone[85] and with azathioprine, antilymphocyte globulin and prednisone[86]; antithymocyte globulin and prednisone[87]; "selective" immunotherapy against activated T cells with the antiblast monoclonal antibody C3L 1,[88] and γ-globulin.[89] While there were no "cures" reported from these trials, patient sample sizes were small, the durations of treatment short and protocols varied greatly. Several editorials reviewing the early immunotherapy trials and addressing the ethical issues of such trials appeared in 1983.[90-92] These issues have centered on the use of "therapeutic" agents with the potential for inducing cancer and infection and disturbing renal function to "treat" a disease, diabetes, in which clinically significant complications were not likely to occur for at least 15 years.

Much more encouraging was an intervention trial in which cyclosporine, a selective T-helper-cell inhibitor, was given for a period of 2 to 12 months to 41 Canadian patients, aged 8 to 49 years, with type I diabetes mellitus.[93] Of 30 patients treated within six weeks of diagnosis, 16, or 53%, became insulin-independent by 196 days of cyclosporine treatment. This contrasted to the achievement of complete insulin independence in only 2 of 11 patients who were similarly treated beginning 8 to 44 weeks after diagnosis. In the early-treatment group, the prevalence of titers of islet-cell cytoplasmic antibodies at diagnosis did not correlate with C-peptide reserve, and recovery of β-cell function occurred despite the presence of ICCA.[95] While the trial was admittedly uncontrolled, the frequency of insulin independence achieved was far greater than the expected 3% of diabetic persons who transiently became insulin-free while receiving conventional insulin therapy[93]; with aggressive therapy using closed- and open-loop insulin delivery systems from diagnosis, insulin-independence rates may be higher.[100] Furthermore, those patients who became insulin independent still had mildly positive glucose tolerance tests and slightly increased glycosylated hemoglobin levels and were treated with oral hypoglycemic agents while off insulin therapy.

In a follow-up publication from the Canadian group, 14 patients were examined from their original cohort who, after treatment with cyclosporine for one year, had their immunosuppressive therapy discontinued.[96] Six of these subjects were insulin-independent at one year, but after the administration of cyclosporine was terminated, five required insulin after a mean of only 72 days; eight subjects who already required insulin after cyclosporine therapy was discontinued needed a significant increase in their exogenous insulin dose after a mean of 36 days. Reversible nephrotoxicity was reported in this study, as has been observed with cyclosporine use in other situations unassociated with primary renal disease, including prevention of heart-transplant rejection[101] and therapy for autoimmune uveitis.[102] Other reversible cyclosporine-induced side effects noted in the Canadian study in-

cluded hyperuricemia, hypertension, hypertrichosis, gingival hypertrophy and nonhemolytic, non-iron-deficient anemia.

A French study—published in abstract form—of 12 patients with the recent onset of type I diabetes showed that administering cyclosporine induced remission (defined as less than 4 units of exogenous insulin per day) in 6/12 subjects, whereas remission occurred in only 3/30 controls.[94] Immunotherapy trials with azathioprine (alone or in combination with prednisone) have now been reported in which remissions have been induced in diabetic patients. Harrison and co-workers found remissions (defined as insulin independence for greater than a week with a fasting blood glucose concentration of less than 7 mmol per liter) in 7/13 azathioprine-treated Australian persons, but in only 1/11 nontreated persons.[98] After 12 months, seven of their azathioprine responders did not require any exogenous insulin, but six became insulin-dependent again within one year. Silverstein and associates reported, in abstract form, insulin independence in five patients treated with azathioprine and corticosteroids (methylprednisolone sodium succinate pulsing initially, followed by prednisone given orally for about three months) and in one patient given only azathioprine.[99] While the Canadian study failed to show differences in C-peptide secretory reserve between insulin-independent and insulin-dependent patients, the French cyclosporine study (at diagnosis) and the Australian azathioprine study (at drug therapy cessation) showed an increase in C-peptide reserve in the responder groups. The significance of these discrepant findings remains unclear.

The need for confirmatory, prospective, controlled and long-term studies was soon realized, and protocols have been initiated in Canada, Miami, Boston and France. The first such report, summarizing the results from the Cyclosporine/Diabetes French Study Group, was recently published.[97] A total of 122 patients with type I diabetes mellitus of recent onset

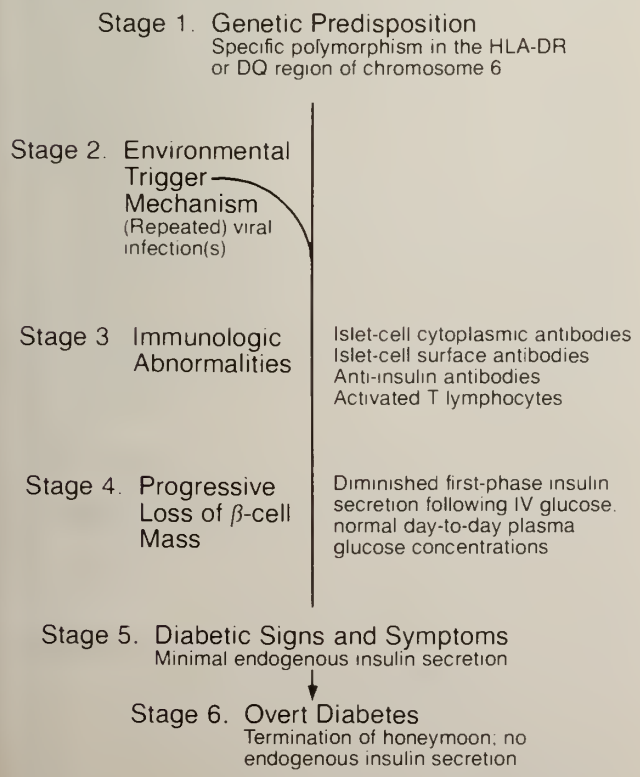

Figure 1.—The evolutionary schema of type I diabetes mellitus.

participated in a randomized double-blind, placebo-controlled study of the efficacy of cyclosporine therapy on the induction of remission associated with insulin independence. Patients were between 15 and 40 years of age, symptomatic for less than six months before diagnosis and had received insulin treatment for less than or equal to two months. Although there were no statistical differences between the frequency of insulin independence in the cyclosporine (25%) and placebo (19%) groups after six months, by nine months patients in the cyclosporine group were significantly more often insulin-independent than those of the placebo group (24% versus 6%; $P < .01$). Remissions were more likely to occur when whole-blood, trough cyclosporine concentrations averaged 300 ng per ml or more during the first three months of treatment. The most noteworthy side effect of cyclosporine use in this study was a modest but reversible rise in the plasma creatinine concentration. Studies correlating the likelihood of remission with residual β-cell function are reported to be in progress. Thus, the results of this study confirm those of previous open human trials[93,94,96] that cyclosporine administration increases the likelihood of clinical remission in patients with type I diabetes.

Summary and Recommendations

The data presented strongly suggest that type I diabetes mellitus is generally an insidious disease resulting from rejection of one's own β-cells. Genetic susceptibility, manifest as an abnormality of immune regulation (both humoral- and cell-mediated), controlled by DNA residing at or near the DR (or DQ) locus on the sixth chromosome, is a prerequisite in almost all cases. An environmental trigger or a series of triggers appears necessary to activate the autorejection of β-cells. This leads to insulin deficiency and the classic signs and symptoms of type I diabetes. The preliminary trials with immunotherapy in persons with newly diagnosed disease have served to underscore the importance of immune mechanisms in inducing β-cell loss.

With this background, Eisenbarth has suggested that type I diabetes mellitus evolves in six stages[72,103,104]; this scheme has been modified and appears in Figure 1:

Stage 1. Genetic susceptibility present from birth.

Stage 2. Environmental triggering due to single or repeated insults.

Stage 3. Specific and nonspecific immunologic abnormalities resulting in an initial loss of β-cells, but with preservation of sufficient insulin reserve.

Stage 4. Slow (?continuous) loss of β-cell mass with maintenance of normal day-to-day plasma glucose levels despite diminished first-phase insulin secretion in response to the intravenous administration of glucose. In this stage, the loss of insulin reserve in response to glucose stimulation appears linear (20 to 40 μU per ml insulin release per year),[105] with relative preservation of β-cell responsiveness to secretagogues that stimulate insulin secretion by receptors presumed different from the "glucoreceptor."[106] Specifically, as also occurs in patients with type II diabetes[107] and in patients with diabetes due to chronic pancreatitis[108] and cystic fibrosis,[109] the damaged β-cell in patients with evolving type I diabetes secretes more insulin in response to nonglucose stimuli, such as arginine, oral glucose (via the enteroinsular axis) and tolbutamide.[105]

Stage 5. With the loss of β-cell mass to 5% to 10% of normal, overt diabetes with its signs and symptoms ensues.

Stage 6. Complete loss of β-cell reserve occurs, signaling the end of any "honeymoon" period.

Because immunotherapy, when applied to the reversal of newly diagnosed diabetes, is not effective in all patients, may require life-long administration and is associated with clear-cut toxicity, alternative strategies need to be developed. One obvious but difficult approach would be the development of an ultraspecific and nontoxic form of treatment aimed, for example, at the attacking arm of the immune system, such as β-cell-specific cytotoxic T lymphocytes. Investigators have attempted to develop predictive laboratory indices in high-risk populations that would allow certain identification of future cases of diabetes so that immune strategies could be applied at an earlier time when β-cell preservation would theoretically be more likely. Unfortunately, immunologic indices may fluctuate and not be reliably predictive, which could result in the hazardous treatment of persons not destined to have diabetes. For the reasons outlined above, routine immunotherapy at or "before" the diagnosis of type I diabetes cannot be considered at this time. Specific protocols designed to examine the potential predictive value of various indices (HLA type, ICCA, ICSA, anti-insulin antibodies, T-cell subsets, activated T cells and the like, or combinations thereof) for the eventual development of type I diabetes mellitus should be pursued. Significantly more research, with an emphasis on molecular identification of the specific predisposing genetic determinants, needs to be undertaken so that future immunologic strategies can be most appropriately targeted.

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Medical Staff Conference

L'Infarctus du Ventricule Droit—Right Ventricular Infarction in the 1980s

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Welcome to our Medical Staff Conference. This again is one of those special occasions when we can honor one of our chief residents, Carlin Long, MD, by giving him the opportunity to educate us at our conference. Carlin is a graduate of Baylor University and the University of Texas Southwestern Medical School where he did research on carnitine deficiency and published several papers. He has been a member of the University of California, San Francisco (UCSF), house staff since 1982 and has distinguished himself by being both a superb teacher and an outstanding clinician. He developed an interest in cardiology, in which discipline he plans to take his fellowship training at UCSF. The subject for discussion today is half in French and half in English, "L'Infarctus du Ventricule Droit—Right Ventricular Infarction in the 1980s."*

CARLIN S. LONG, MD:† Acute myocardial infarction, occurring in nearly 1 million patients in the United States each calendar year, affects predominantly the left ventricle. Furthermore, the complications we normally discuss relative to acute infarction, namely pump failure and tachyarrhythmias, have invariably been tied to left ventricular dysfunction. While not as common as left ventricular infarction, right ventricular infarction is not rare and is a subject well worth reviewing for a general medical audience.

I am going to briefly discuss the incidence, pathology and pathogenesis of right ventricular infarctions, but will spend the most time on discussing the diagnosis and the treatment. I would like to address four issues: How frequently does right ventricular infarction occur, under what circumstances does it occur, how is the diagnosis made and how should it be treated?

The role of the right ventricle in maintaining both normal hemodynamics and hemodynamics in cases of acute infarction has been realized only in the past decade. Much of the anonymity that the right ventricle had before that time was the result of experimentation done in the mid-1940s. Starr and colleagues, using an open-chest dog model, created right ventricular dysfunction and destruction, but found no change in either venous or arterial pressures. They concluded that the right ventricle had very little to do with normal hemodynamics and that it could, in fact, be destroyed without much ill effect.[1] This attitude prevailed despite some animal research[2,3] until the clinical report of Cohn and co-workers in 1974 that suggested that right ventricular infarction in humans may not be as innocuous as the initial reports implied.[4]

Incidence

In an early series of 2,000 autopsies (1948), 160 patients had evidence of left ventricular infarction; only 22 (14%) of these had evidence of simultaneously occurring right ventricular infarction.[5] Isolated right ventricular infarction occurred in less than 2% of these patients. In a later series of 84 patients selected from those who died in a coronary care unit as a result of their infarction, 36 (43%) had autopsy evidence of right ventricular infarction.[6] In a series of 236 patients with transmural infarcts of whom 139 had posteroinferior wall infarcts, right ventricular infarction was found in 33 (24%) and only in the setting of posteroinferior wall left ventricular infarctions.[7] The amount of right ventricular myocardium involved was classified pathologically as grades I and II (involvement of the posterior wall of the right ventricle) and grades III and IV (extension onto the anterolateral free wall of the right ventricle) (Figure 1). Of note is that 80% of the patients in this series fell into grades I and II. Subsequently, grade V was added to describe those with isolated anterolateral wall involvement.[8] Table 1 shows a summary of these and other papers in the literature that address the incidence of right ventricular infarction. The mean incidence is 23%.

Pathogenesis

Right ventricular hypertrophy has been described as occurring with a threefold higher incidence in patients with right ventricular infarction as compared with a group of patients with isolated left ventricular infarction, suggesting that this might be cause and effect and not merely a chance observation.[10] In experimental right ventricular hypertrophy produced by banding the pulmonary artery, constriction of the right coronary artery caused right ventricular infarcts in 80% of the animals, compared with only 10% in control animals without prior right ventricular hypertrophy.[2] This observation that virtually all right ventricular infarctions occur in the group with right ventricular hypertrophy has been confirmed and also extended to show that by 21 days, left-to-right collaterals were found in less than 60% of the animals with infarcts as compared with 100% in the control animals subjected to only slow right coronary occlusion.[3] Thus, both poor coro-

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(Long CS: L'infarctus du ventricule droit—Right ventricular infarction in the 1980s [Medical Staff Conference]. West J Med 1987 Mar; 146:344-350)

TABLE 1.—*Summary of Incidence of Right Ventricular (RV) Infarction From Autopsy Data**

Authors	Patients With RV Infarction/Autopsies, No./No. (%)
Lisa and Ring, 1932	22/160 (14)
Bean, 1939	95/287 (33)
Wartman and Hellerstein, 1948	22/160 (14)
Laurie and Woods, 1963	13/99 (13)
Erhardt, 1974	36/87 (41)
Isner and Roberts, 1978	33/236 (14)
Ratliff and Hackel, 1980	35/102 (34)
Total	256/1,131(23)

*From Nixon.[9]

TABLE 2.—*Pathogenesis of Right Ventricular Infarction*

- Predominantly a right coronary artery occlusion with an inferior or inferoposterior infarction
- Patients with preexisting right ventricular hypertrophy are probably at increased risk
- Patients with 3-vessel disease and "inadequate" left-to-right collateral formation are also probably at increased risk

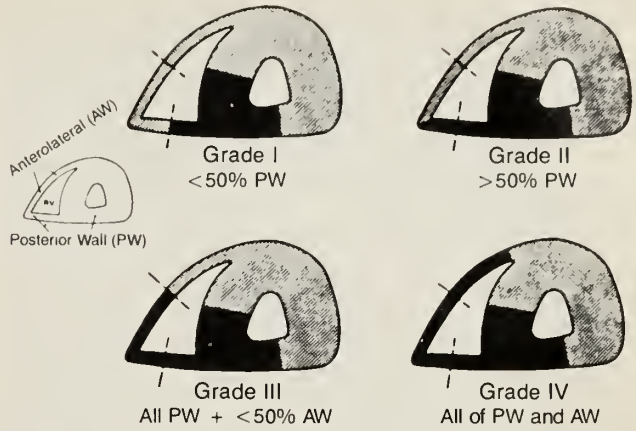

Figure 1.—Diagram of transverse slices of cardiac ventricles showing the grading of extent of right ventricular (RV) infarct. The right ventricular infarct was classified as grade I when it involved less than 50% of the posterior wall of the right ventricle; grade II when it was limited to the posterior wall but involved more than 50% of it; grade III when it involved all of the posterior wall and some, but less than 50% of its anterolateral wall, and grade IV when it involved all of the right ventricular posterior wall and more than 50% of the anterolateral wall (from Isner and Roberts[7]).

nary anastomoses and right ventricular hypertrophy seemed to be responsible for right ventricular infarction, though there was not a direct correlation with the amount of ventricle involved in the infarction. In later studies of autopsies of 19 patients who died with evidence of right ventricular infarction, the extent of ventricular involvement was directly related to obstruction to flow from left to right as judged by postmortem injection of the coronary arteries.[11] In another study 48 patients who died with a diagnosis of chronic obstructive pulmonary disease were divided pathologically into three groups: group 1A (n=14) had chronic obstructive pulmonary disease and at autopsy had no evidence of right ventricular hypertrophy but did have evidence of an inferior wall left ventricular infarct. Group 1B (n=14) had both right ventricular hypertrophy and evidence of an inferior infarct. Group 2 (n=20) had evidence of right ventricular hypertrophy but none of an infarction. The group of patients who had the highest percentage of right ventricular involvement were those who had simultaneously occurring right ventricular hypertrophy and coronary artery disease as evidenced by inferior wall left ventricular infarction at postmortem examination.[12]

In summary, for the development of right ventricular infarction (Table 2), one expects to see predominantly a proximal right coronary artery occlusion with an inferior wall left ventricular infarct. Patients with preexisting right ventricular hypertrophy are probably at increased risk, as are patients with severe three-vessel disease and without adequate left-to-right collateral formation.

Making the Diagnosis

Clinical Examination

In 1974 Cohn and co-workers published what many believe to be the landmark clinical article on right ventricular infarctions.[4] While doing routine hemodynamic monitoring in 78 patients with acute infarction, they found six patients who presented a characteristic clinical picture. All had inferior wall infarcts; all presented with systolic blood pressures of less than 90 mm of mercury. Five out of six were clinically in shock with cool, clammy extremities. All six had evidence of venous engorgement by physical examination, but four of the six had no abnormalities found on chest examinations on admission. Postmortem examination in the two who died showed extensive right ventricular infarction. The authors concluded that right ventricular infarction occurred in cases of inferior wall left ventricular infarctions and produced a unique clinical constellation of hypotension, shock, venous engorgement and yet a clear chest.

In a prospective series of 16 patients with inferior wall infarcts and in whom there was clinical evidence of right ventricular dysfunction, most had right-sided S_3 gallops.[13] Many had jugular venous pressure distention and, curiously

TABLE 3.—*Sensitivity and Specificity of Physical Findings in Hemodynamically Significant Right Ventricular Infarction**

	Elevated JVP, (>8cm of water), %	Kussmaul's Sign, %	Elevated JVP and Clear Lungs, %	Elevated JVP and Systemic BP <100mmHg and Clear Lungs, %	Elevated JVP and Kussmaul's Sign, %
Sensitivity	88	100	50	25	88
Specificity	69	100	82	96	100

BP = blood pressure, JVP = jugular venous pressure

*From Dell'Italia et al,[15] used with permission.

TABLE 4.—*Clinical Findings Associated With Right Ventricular Infarction**

Elevated jugular venous pressure
Hypotension
Kussmaul's sign
Abnormal jugular venous pressure pattern (Y > X descent)
Right-sided S_3 and S_4

*Adapted from Dell'Italia and Starling [16]

enough, all had evidence of Kussmaul's sign—absence of the expected fall in jugular venous pressure with inspiration. It was concluded that Kussmaul's sign, which is usually seen with pericardial constriction, was a sensitive indicator of right ventricular involvement in a case of inferior wall infarct. Kussmaul's sign has been reported in 81% (30) of 37 patients with inferior infarctions who consented to hemodynamic monitoring.[14]

The sensitivity and specificity of two isolated physical findings have been evaluated (Table 3), those of elevated jugular venous pressure and any one of a number of other physical findings: clear lungs, hypotension or a positive Kussmaul's sign.[15] If an elevated jugular venous pressure (greater than 8 cm of water) and a positive Kussmaul's sign were present, the sensitivity and specificity of hemodynamically significant right ventricular infarction was between 80% and 100%. Table 4 gives a summary of clinical findings associated with right ventricular infarcts. Of some interest is the finding of a y descent greater than the x descent in the jugular venous pressure tracing, confirmed by Swan-Ganz measurements from the right atrium.[17] The most easily detectable and sensitive clinical findings are, of course, an elevated jugular venous pressure and the presence of Kussmaul's sign.

The Electrocardiogram

Once the history and physical examination are completed, the next noninvasive test usually available to all physicians is the electrocardiogram. Right precordial electrocardiography shows ST-segment elevation in many of these patients.[6,18] In a study of 33 patients with acute myocardial infarcts, 11 had at least 1 mm of ST-segment elevation in either the V_{4R}, V_{5R} or V_{6R} lead (the mirror image of the left precordial leads traced out on the right chest) and 22 did not.[18] In the former group, nine had pyrophosphate scans positive for right ventricular infarction as compared with only one in the latter group. From these data, Croft and associates suggested that the sensitivity, specificity, accuracy and positive predictive value of ST-segment elevation occurring in one of these three leads was between 80% and 90%.[18] In another study of right precordial electrocardiography of 110 patients with inferior wall infarcts, 58 were felt to have right ventricular infarcts defined by either right ventricular dilation, positive pyrophosphate scan, elevated right ventricular end-diastolic pressure or by postmortem examination (n=4).[19] In this group of 58 patients, 48 had an ST-segment elevation of 0.5 mm or more in the single V_{4R} right precordial lead. In comparison, 40 of the 52 without right ventricular infarction had no ST-segment elevations. Again, the calculated sensitivity, specificity and positive and negative predictive values were about 80%. In a group of 30 patients who died of inferior infarction, 21 had right ventricular involvement.[20] Of these 21 patients, 16 had ST-segment elevation in V_{4R}; furthermore, of the 17 patients who did not have an underlying interventricular conduction delay (in other words, a normal QRS duration and morphology), 13 had both ST-segment elevation and the development of a Q wave or a QS complex in the V_{4R} lead.[20] Morgera and co-workers suggested that, similarly to what we expect in left ventricular infarctions, a Q wave could be pathognomonic of infarcted tissue. Again, both the sensitivity and specificity of these findings were approximately 80%.[20] To validate their observation, they looked at the incidence of Q waves in 82 patients without cardiopulmonary disease: 2.4% had Q waves in lead V_{4R} and none had a Q wave in lead V_{3R}, suggesting that when these occur they are pathologic.

In a study of patients at risk for having right ventricular involvement with inferior wall infarcts, in whom radionuclide angiography showed a diminished right ventricular ejection fraction (a mean of 30% compared with 42% seen in their control patients with inferior wall infarcts), Lew and colleagues reported the ratio of reciprocal ST-segment depression anteriorly (V_1) to ST-segment elevation in the inferior leads (aV_F) to be useful.[21] Invoking a vectorcardiographic approach, they suggested that the ST-segment depression anteriorly is elevated by an underlying right ventricular infarct in contrast to the finding in those patients who had no right ventricular involvement, yielding a ratio of less than the control value of 0.5.

Echocardiography

One of the other noninvasive tools available to most clinicians early in the workup of acute infarctions is the echocardiogram. Initially, M-mode echocardiograms in patients with inferior wall infarcts showed promise in distinguishing between those patients who had right ventricular involvement and those who did not, in that the former patients had ratios of greater than 0.5, whereas in the latter the ratio was less than 0.5.[22] Those patients with isolated anterolateral infarcts similarly had ratios that were less than 0.5. More recently, using two-dimensional echocardiography in a series of 228 patients with acute infarcts in whom 91 were localized to the inferior wall, 31 patients had right ventricular involvement defined by venous congestion, hypotension and a clear chest. Of those patients in whom the endocardium of both left and right ventricular cavities was seen, all had right-to-left ventricular end-diastolic diameter ratios of greater than 0.5, as noted previously.[23] Furthermore, all of them had evidence of segmental right ventricular wall motion abnormalities in addition to their expected inferior wall abnormalities.[23,24]

Scintigraphic Studies

Similar to echocardiography, radionuclide angiography frequently shows right ventricular dysfunction in patients with acute inferior wall infarcts. In an early series of 78 patients presenting with acute inferior wall infarcts evaluated with both thallium and pyrophosphate scanning, 11 had thallium scans positive for inferior infarcts, and of the 64 with positive pyrophosphate scans, 24 (38%) had evidence of both left and right ventricular uptake.[25] These findings have been reproduced by others[22,26] and expanded to include the radionuclide determination of ejection fractions showing substantial impairment in the right ventricular ejection fraction (usually less than 40%) in those patients with right ventricular involvement compared with those patients with isolated anterolateral infarcts (ejection fraction usually 50% or greater).[24,26-28]

Table 5 summarizes the criteria for the noninvasive diag-

nosis of right ventricular infarction in the three most commonly used modalities: electrocardiography, echocardiography and radionuclide angiography. Because many of these patients come to Swan-Ganz catheterization for management and diagnosis, no discussion of right ventricular infarctions would be complete without reviewing the invasive findings in these patients.

Hemodynamics

In one of the first reports of routine hemodynamic measurements in patients with acute infarcts, it was noted that a few patients were set apart on the basis of elevated right ventricular end-diastolic pressures in comparison to pulmonary arterial pressure. It was of "some interest" that these patients were also "similar clinically in that all belonged to the supraventricular bradycardia group with vasovagal episodes and a posterior setting of the infarct."[29(755-756)] It was questioned "whether raised end-diastolic pressure in these patients reflected involvement of the right ventricle in the process of infarction."

Soon after this first report, Cohn and colleagues reported on the hemodynamic findings in six infarction patients who presented with what was felt to be pronounced right ventricular involvement.[4] These six were set aside from the rest of the patients with acute infarcts in that for any given left ventricular filling pressure there was a substantial elevation in the right ventricular filling pressure (Figure 2). Furthermore, in a series of 54 patients with right ventricular dysfunction and acute inferior wall infarcts, defined by a ratio of right atrial to capillary wedge pressure of greater than 0.8, 40 (74%) were found to have a "noncompliant pattern" in both right atrial and jugular venous pressure patterns in that the y descent was much steeper than the x descent, this being the hemodynamic counterpart of the positive Kussmaul's sign seen on physical examination.[17] It has also been noted that the ratio of right atrial to capillary wedge pressure in all of these patients is abnormally high (approaching 1) compared with in those patients who do not have evidence of right ventricular involvement (about 0.5). Furthermore, most have elevations in right atrial pressure (mean of approximately 15 to 16 mm of mercury) compared with patients without right ventricular infarction who have diminished cardiac indices and a right ventricular stroke work index when calculated.[15] Of some interest is the observation in a series of 53 patients with inferior infarcts that only 8 had initial criteria for right ventricular involvement (right atrial pressure 10 or more mm of mercury; right atrial to capillary wedge pressure ratio greater than 0.8); 27, however, started with a capillary wedge pressure of less than 15 mm of mercury. After an infusion of fluids was given intravenously to raise the capillary wedge pressure to 15 mm of mercury, an additional six patients who then met the criteria for right ventricular infarction were uncovered, suggesting that volume loading may be beneficial in "uncovering" a patient with right ventricular involvement who has inferior wall infarction.[15]

In summary, the invasive diagnosis of right ventricular infarction is made by the criteria listed in Table 6. A resting right atrial pressure of greater than 10 mm of mercury is expected, as well as a right atrial to capillary wedge pressure ratio of greater than or equal to 0.8 in the presence of a capillary wedge pressure of at least 15 mm of mercury. When a capillary wedge pressure is initially less than 15 mm of mercury, volume should be judiciously loaded to a value of 15 mm of mercury and the measurements repeated. Also expected are evidence of a "noncompliant" pattern in the right atrial pressure tracing (y greater than x descent) and a diminished right ventricular stroke work index.

TABLE 5.—*Noninvasive Diagnosis of Right Ventricular (RV) Infarction*

Electrocardiography
- Inferior or inferoposterior wall infarction
- ST-segment elevation ≥ 0.5 mm (with or without a QS complex) in lead V_{3R} or V_{4R}
- ?ST-segment depression in lead V_1 less than 50% of ST-segment elevation seen in aV_F

Echocardiography
- Ratio of RV end-diastolic diameter to LV end-diastolic diameter > 0.5
- RV chamber dilation with diminished percentage of fractional shortening
- RV segmental wall motion abnormalities

Radionuclide Studies
- Positive pyrophosphate scan (anterior to the septum in the retrosternal space)
- RV ejection fraction by either first pass or equilibrium wall motion study < 40%
- RV regional wall motion abnormalities

LV = left ventricular

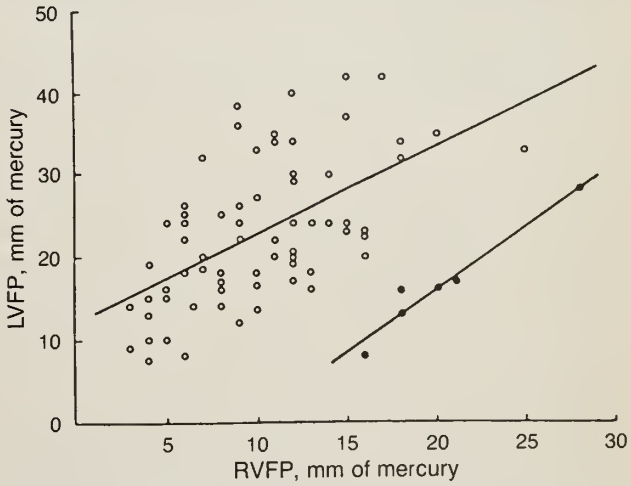

Figure 2.—Simultaneous right ventricular filling pressure (RVFP) and left ventricular filling pressure (LVFP) in patients with acute myocardial infarction. Open circles represent values in 72 patients with predominantly increased left ventricular filling pressure; closed circles represent 6 patients with predominantly increased right ventricular filling pressure. Regression lines for the two groups have been drawn (from Cohn et al[4]).

Treatment

Following the initial reports on the benefits of volume loading[30] in animals with experimentally induced right ventricular infarction, this therapy was applied to the treatment of right ventricular infarction in patients.[31-34] In an early series of 36 patients with inferior infarcts and right ventricular dysfunction (defined by an elevated right atrial pressure and an elevated ratio of right atrial pressure to pulmonary capillary wedge pressure), 16 had an initial cardiac index of greater than 2.2 liters per minute per m^2—felt to be adequate in patients with acute infarcts[32]—and 20 patients had an initial index of less than this.[31] When dextran 40 was infused at 100 ml per minute for a 5 mm of mercury increase in the right atrial or capillary wedge pressure, only 50% of the group of

TABLE 6.—*Invasive Test Findings With Right Ventricular (RV) Infarction*

Resting right atrial pressure (RAP) greater than 10 mm of mercury with an RAP:pulmonary capillary wedge pressure (PCWP) ratio of greater than 0.8 in the presence of a PCWP of greater than 15 mm of mercury
For an initial PCWP of less than 15 mm of mercury, an intravenous infusion of fluids is administered to bring PCWP to 15 mm of mercury with repeat RAP:PCWP calculation
Evidence of a "noncompliant" pattern in the RAP tracing (y greater than x descent)
Diminished RV stroke work index less than 5 grams • m per m^2

TABLE 7.—*Treatment of Right Ventricular Infarction*

Avoid the use of preload reducing agents—that is, diuretics, especially those given IV
Administer fluids IV for "optimal" cardiac index, aiming for right atrial pressures and pulmonary capillary wedge pressures of 15 mm of mercury or greater but no more than 20 mm of mercury
In the absence of a normal cardiac index by the above methods, dobutamine hydrochloride should be infused
Consider atrial or atrioventricular pacing especially if there are complicating bradyarrhythmias
? Consider thrombolytic therapy in cases of inferior wall myocardial infarction complicated by right ventricular involvement
IV = intravenously

patients with an initial cardiac index of less than 2.2 liters per minute per m^2 had indices that rose above this adequate level (mean of 2.78). Furthermore, all five deaths in this series were in those patients in whom no rise in cardiac index was achieved with dextran infusion. This experiment established the "optimal" right atrial and capillary wedge pressures for patients with right ventricular involvement, suggesting that the highest cardiac index occurred when both pressures were maintained at somewhere between 15 and 20 mm of mercury.

Later, experiments were carried out that helped explain why not all of these patients improve with volume infusion.[33] Using a closed-chest (and pericardium) dog model, right ventricular infarctions were produced by injecting a mercurial compound into the right coronary artery. At autopsy, all animals had evidence of right ventricular infarction. It was observed that from control to postinfarct in an animal with an intact pericardium, the mean arterial pressure fell dramatically and was accompanied by a raised right ventricular end-diastolic pressure, a reciprocally diminished left ventricular end-diastolic pressure and a greatly diminished stroke volume and cardiac output. If then infused with a saline solution, the mean arterial pressure was increased, but only at the expense of higher right and left ventricular end-diastolic pressures. Stroke volume and cardiac output, although improved, did not reach control values; furthermore, the heart rate went up considerably to account for most of the increase in cardiac output. If a pericardiotomy was then done in these animals, the mean arterial pressures fell and both stroke volume and cardiac output improved to beyond control levels. In patients with right ventricular infarction, the pericardium thus becomes functionally constricting in that left ventricular filling and hence cardiac output are diminished and volume is responsive only to a point. Obviously a pericardiotomy cannot be done in most patients presenting with this clinical disorder and thus research has been turned to other, more practical means of therapy.

Recently Dell'Italia and associates looked at the pharmacologic therapy for right ventricular infarction complicating inferior wall infarction in 13 patients.[34] They did base-line hemodynamics and, in those patients whose capillary wedge pressure was less than 15 mm of mercury (n = 10), volume loading was done to a capillary wedge pressure of 15 mm of mercury, and both hemodynamics and wall-motion studies were repeated. Dobutamine hydrochloride was then infused for an end point of mean arterial pressure or heart rate increases of 10% from base line, and subsequently sodium nitroprusside was infused as an afterload reducing agent for an end point of a mean arterial pressure drop or heart rate increase again 10% from base line. They repeated hemodynamics and wall-motion studies after each maneuver. Neither saline solution nor sodium nitroprusside administration resulted in a statistically significant improvement. With dobutamine infusions, however, there was a substantial increase in mean cardiac indices from 2.1 to 2.8 liters per minute per m^2. They concluded that in patients with right ventricular involvement and inferior infarctions,

> volume infusion should be used to achieve an increase of greater than 5 mm of mercury not to exceed 20 mm of mercury in both capillary wedge or right atrial pressures, [that the] initial volume infusion should be carefully administered and if cardiac output did not improve, dobutamine be administered to augment right ventricular systolic performance and improve forward cardiac output.[34(p1334)]

In addition to this pharmacologic approach, two groups of investigators published studies of patients with an inferior wall infarct with right ventricular involvement in whom a symptomatic bradycardia was noted.[35,36] With pacemaker therapy they observed that cardiac output improved with ventricular pacing, but improved even more dramatically with atrial or atrioventricular sequential pacing. This suggests that in patients with right ventricular infarction and dilated, poorly contractile right ventricles, the dependence of right ventricular output on atrial contraction (preload) is considerable, and these patients may benefit from atrial or atrioventricular sequential pacing, especially when there are complicating bradyarrhythmias.

Turning to thrombolytic therapy, recently Schuler and coworkers looked at 19 patients with inferior wall infarcts and right ventricular involvement given streptokinase, 12 of whom were found to have recanalization of their occluded right coronary arteries.[37] Four weeks after acute infarction, those patients who had recanalization showed a pronounced improvement in their right ventricular ejection fraction compared with those who did not (43% versus 32%). Furthermore, all deaths occurred in those patients who failed to have recanalization, suggesting that in a patient who has an inferior wall infarct with right ventricular involvement, streptokinase therapy can be beneficial and, in fact, if successful may improve the prognosis. This is the only experiment addressing thrombolytic therapy in this subgroup of patients and should be looked at in a more controlled fashion before being recommended as standard therapy for patients with right ventricular infarction.

Table 7 summarizes the most logical approach to the treatment of right ventricular infarction at the present time. Because the right ventricle is extremely volume (preload) sensitive, preload-reducing agents that will further diminish the right ventricular filling pressure should be avoided. Obviously furosemide given intravenously is a big offender, as are morphine and nitrates; one often cannot avoid using the last two in these patients, but the use of furosemide can sometimes

be avoided, at least immediately after the infarction. The tendency when a patient has an inferior wall infarct and evidence of jugular venous pressure distention, despite having a clear chest, is to give furosemide. Because, however, this can diminish the right ventricular filling pressure in a patient with right ventricular infarction, it may, in fact, precipitate a crisis of low left ventricular filling pressure and output. One should provide fluids intravenously for an optimal cardiac index (usually a right atrial or capillary wedge pressure of greater than 15 mm of mercury and less than 20 mm of mercury). In the absence of a normal cardiac index by the volume infusion method, a regimen of dobutamine should be promptly started. The use of atrial or atrioventricular sequential pacemaker therapy should be considered, especially when there are complicating bradyarrhythmias. Whether or not streptokinase should be used in this clinical setting needs further research.

Summary

In summary, right ventricular dysfunction is not rare; it occurs in about 20% of all cases of infarction and in as many as 35% of all cases of inferoposterior infarctions. The diagnosis can be suggested (and nearly refuted) strictly on the basis of a careful physical examination and confirmed by the results of a number of noninvasive tests readily available to most physicians. Hemodynamic monitoring can likewise be diagnostic and of help in managing these cases. Therapy is aimed at maintaining right ventricular filling pressures and output, as this directly determines left ventricular output. As with many things in medicine, perhaps the most important point concerning this unique clinical disorder is maintaining a high index of suspicion for its occurrence.

Questions and Answers

DR ROOT: We have time for questions.

PHYSICIAN IN THE AUDIENCE: *In the patients who recanalized following streptokinase therapy, what was predictable for the ultimate success—time after infarct, or something else?*

DR LONG: All of these patients presented within four hours of the onset of pain, so they were in the group of patients who we normally consider to be presenting in time to get streptokinase infusions. There was in fact no prediction of who would have recanalization versus who would not, only that both short- and long-term improvement in right ventricular performance was only seen in those patients with documented reperfusion.

PHYSICIAN IN THE AUDIENCE: *The slide that you showed by Goldstein suggested that the pericardium was a large source of the hemodynamic problem seen in patients with right ventricular infarct. Do you see pericardiectomy as a possible short-term therapy in these patients?*

DR LONG: The numbers do suggest that right ventricular output and then left ventricular output improved dramatically with that intervention. I am hesitant to say that pericardiectomy would be an option for us in a coronary care unit when there are other things that are clearly available, namely adding volume, giving dobutamine and pacemaker therapy, when necessary.

I suppose in an extreme case of a patient who was not responsive to any of these modalities, one might consider doing pericardiectomy, although the timing for this is critical. Usually patients with an acute infarction of only the left ventricle who are doing poorly, and those with right ventricular involvement, are those patients who have severe three-vessel disease with diminished left ventricular output and who are destined to do badly.

PHYSICIAN IN THE AUDIENCE: *Could you comment on the occurrence of ventricular ectopy or arrhythmias in isolated right ventricular infarction?*

DR LONG: I did not have the time to address this complication of right ventricular infarction. It is a topic that could by itself be a Medical Staff Conference presentation. Some people think that right ventricular infarctions lead to a higher incidence of arrhythmias. Sclarovsky and associates looked at 30 patients with infarct who required temporary pacemaker therapy.[38] In this series, five cardiac arrests due to ventricular fibrillation occurred, and all five were in patients who had right ventricular involvement with an inferior wall infarct. These retrospective data suggest that the right ventricle is very irritable when it is involved in an infarct. Other data from experiments with animals suggest that if one ties off the right coronary artery and produces right ventricular infarction, 100% of the animals have spontaneous ventricular tachycardia or ventricular fibrillation within the first 24 hours.[39,40] If these animals are studied three days after infarction when they are not having spontaneous ectopy, one can induce sustained ventricular tachycardia in a higher percentage of animals with right ventricular involvement than in those that do not have right ventricular involvement (up to 70%). This has not been looked at in a large-scale study of humans, but certainly the data are suggestive that, similar to right ventricular dysplasia, there seems to be an increased arrhythmogenic potential in patients who have right ventricular involvement.

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Epitomes

Important Advances in Clinical Medicine

Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Neurologic Consequences of Designer Drugs

What are "designer drugs"? Most simply put, they are analogs of controlled substances (or CSAs, as we now call them). Historically, they can be viewed as the penultimate result of the synthetic drug revolution that began in the 1960s with LSD and phencyclidine hydrochloride (PCP). These new compounds are legal to possess, cheap to produce and do not have to be imported. The subject is a timely one in view of current efforts to stem the flow of illicit narcotics into the United States. If successful, this well-intended effort is likely to result in an explosion of domestically produced "synthetics." These compounds can be sold under almost any guise, including heroin, cocaine and even as marijuana (parsley laced with PCP).

There are three reasons why physicians should be concerned. Some of these compounds are extraordinarily potent, increasing the risk of overdose, particularly in the hands of a novice. One of the fentanyl analogs sold on the street, for example, is known to be 1,000 times more potent than morphine. Second, to the best of my knowledge, none of the "kitchen chemists" has ever been credited with testing a newly synthesized product on laboratory animals before releasing it for human consumption. Hence, the danger that a new toxin may "hit the street" is ever constant. Finally, quality controls are lacking. Bad batches are usually first discovered when addicts get sick.

Given the foregoing, it is not surprising that CSAs have spawned a rapidly developing branch of neurotoxicology. The first selective neurotoxin sold in California as heroin was 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (now widely known as MPTP), which appeared on the streets in 1982. MPTP selectively destroys the zona compacta of the substantia nigra and causes parkinsonism in its victims. Although there are only seven known severely involved patients with MPTP-induced parkinsonism, epidemiologic evidence suggests that more than 500 young addicts may have injected MPTP under the impression it was heroin. Hence, MPTP-induced parkinsonism should be considered in the differential diagnosis of any person with an early case of parkinsonism and a history of drug abuse.

Parkinsonism is not the only neurologic complication to result from the increasing flow of synthetic street drugs. In the past six months more than 20 cases of chorea of varying duration have been identified in persons abusing amphetamine. While amphetamine-induced chorea has been reported previously, it is rare, and the sudden appearance of a number of new cases has raised concern that a much more potent, new "designer" amphetamine may have appeared on the drug scene. Efforts are currently under way to further characterize this syndrome and identify the offending agent. For the moment, however, the acute onset of chorea in young adults should at least raise the question of amphetamine-analog abuse.

There are other analogs of amphetamine that may be equally worrisome. Methamphetamine, MDA (3,4-methylenedioxyamphetamine) and MDMA (3,4-methylenedioxymethamphetamine; "ecstasy") appear to be neurotoxic, causing prolonged depletion of serotonin and nerve terminal degeneration in the striatum and hippocampus of laboratory animals. While the clinical implications of these effects have yet to be determined, these observations provide one more cause for concern regarding the effects of synthetic drug abuse.

If there is a message in all of this, it is that physicians need to be increasingly aware of the medical hazards of the synthetic drug revolution that appears to be rapidly descending on us.

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Immunotherapy in Multiple Sclerosis

Multiple sclerosis remains a disorder of unknown pathogenesis despite decades of research. Current immunologic studies imply both humoral and cellular immune dysfunction. These findings have raised the possibility of an autoimmune basis for this disease, but conclusive proof is lacking. The presumed immune dysfunction, however, forms the basis for

various currently available immunotherapies. The following treatments are now accepted in clinical practice, but should be undertaken with the guidance of a neurologist familiar with the use, risks and side effects of these methods.

Cyclophosphamide

During the past five years, several studies have investigated intensive immunosuppressive treatment with cyclophosphamide in patients with multiple sclerosis. Initial trials showed that about 75% of patients with chronic progressive disease received benefit defined as stabilization or abatement of clinical symptoms for a year. A recent five-year follow-up of 188 patients who received cyclophosphamide treatment showed reprogression in 87%, necessitating retreatment. The most recent treatment programs now involve an induction regimen followed by periodic outpatient booster injections of cyclophosphamide to maintain remission.

Corticosteroids

Long a mainstay in treating patients with relapsing or remitting multiple sclerosis, corticosteroids have shown efficacy in a new double-blind trial of high doses of parenterally administered methylprednisolone sodium succinate. The drug was administered intravenously in an initial dose of 15 mg per kg per day, tapering to 1 mg per kg per day in 15 days, followed by a course of prednisone given orally in decreasing doses over four months. Treatment with methylprednisolone was associated with significantly greater improvement and a shorter relapse duration than in control patients.

Azathioprine

Prolonged administration of azathioprine has been used in cases of nonremitting multiple sclerosis since the 1970s. The results of clinical trials have been mixed. Some of the studies were uncontrolled, making interpretation difficult. The combined use of azathioprine and methylprednisolone may slow the progression of the disease, according to a new three-year study conducted at UCLA. Side effects of azathioprine use include leukopenia and liver function abnormalities in some patients.

Plasmapheresis or Lymphocytapheresis

Reports that humoral and cellular factors may be involved in multiple sclerosis have resulted in trials of plasmapheresis and lymphocytapheresis. Previous studies of plasmapheresis have given mixed results, and some studies have combined the use of plasmapheresis with a regimen of prednisone given orally and cyclophosphamide. A multicenter, double-blind study of plasmapheresis and immunosuppression will be completed this year. Lymphocytapheresis as a long-range therapy has been tested in a one-year trial and has shown no clear benefit. As of this writing, there are insufficient data to recommend these two therapies in patients with multiple sclerosis.

Treatments Under Investigation

In the opinion of some experts on multiple sclerosis, patients should not be treated with investigational drugs outside of experimental protocols. A number of treatment regimens are currently under investigation and these include natural and recombinant interferon, cyclosporine, monoclonal antibodies against T-lymphocytes and poly-ICLC, a potent interferon inducer.

In summary, a number of immunotherapies are currently available or under investigation for multiple sclerosis, but the risks, side effects and benefits of these treatment measures should be carefully weighed in each case with guidance from a neurologist familiar with the treatment of this disorder.

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Pseudoseizures

PSEUDOSEIZURES are characterized by paroxysmal behavioral alterations that may resemble epileptic seizures. Impaired responsiveness to external or internal stimuli (or both) and involuntary movements, often dramatic, are common features. Pseudoseizures are often a conversion symptom ("hysterical seizures") and may coexist with other neurologic or nonneurologic illnesses. In addition to epileptic seizures, other neurologic disorders, such as narcolepsy and migraine, or certain cardiovascular and systemic conditions, particularly syncope, must be excluded before pseudoseizures are considered. Further, the relationship between pseudoseizures and psychiatric illnesses has been poorly defined.

Because patients are rarely examined during an actual attack and are often amnestic of the ictal events, the diagnosis of pseudoseizures is taxing to a clinician. In an atmosphere of defensive medicine, practitioners are more inclined to initiate antiepileptic drug treatment than to resort to further observation when diagnostic tests are negative and the question cannot be resolved. Because of the chronicity of epilepsy that they mimic, pseudoseizures often become a chronic, disabling illness. It has been shown that a significant number of epilepsy victims also have pseudoseizures. Consideration of this disorder is important in managing epileptic seizures not only at the onset but also in refractory cases. Antiepileptic drug intoxication may aggravate pseudoseizures.

The diagnosis of pseudoseizures owes much to the increased accuracy in diagnosing epileptic seizures. It is now feasible to extend an electroencephalographic (EEG) monitor to critically examine a clinical attack. In many instances, an ambulatory cassette EEG monitor may be preferable because it does not require hospital admission. This method, however, cannot provide reliable information concerning the ictal behavior. Prolonged monitoring and documentation of a patient's behavior can only be accomplished in a hospital setting, most commonly in conjunction with a video monitor system. EEG and video data can be played back later simultaneously for detailed analysis. Such an approach is considered essential in diagnosing pseudoseizures in patients who also suffer genuine epileptic seizures.

One must realize in this diagnostic undertaking that an absence of abnormalities, even when monitoring is prolonged, does not by itself establish a diagnosis of pseudoseizures. Inducing an attack by suggestion or in a specific provocative environment is an effective means of aiding the investigation. The precipitation of genuine epileptic seizures under certain controlled circumstances, however, including

psychologically structured interviews, has been well documented. Measuring the serum prolactin level immediately following an attack has been advocated as a diagnostic aid and, when elevated, may prove useful in confirming epileptic seizures.

There is no widely accepted effective treatment for pseudoseizures. There has been a renewed interest in the use of hypnosis, but its effectiveness in this disorder must be carefully evaluated in a controlled fashion. Therefore, an accurate diagnosis remains the single most important step in managing pseudoseizures.

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Should Hypertension in a Patient With Acute Stroke Be Treated?

COMMON MEDICAL WISDOM, still widely taught and believed in this country, holds that elevated blood pressure should be lowered during ischemic stroke and certain other cerebrovascular disorders. Although this dogma has been questioned in recent years, most practicing physicians still use antihypertensive measures immediately after cerebral infarction and in patients with subarachnoid or intracerebral hemorrhage.

High blood pressure is very common early in the course of acute stroke, being found in 70% or more of these cases when seen initially. Of those patients not treated for hypertension, the great majority become normotensive within ten days. The blood pressure rise associated with the onset of cerebral ischemia apparently subsides as brain function recovers and autoregulation is restored. In such persons a sudden new blood pressure elevation may suggest a recurrence of brain ischemia. Bilateral carotid occlusion in animals is accompanied by an immediate rise in the blood pressure, which generally is proportional to the fall in cerebral perfusion. These observations indicate that hypertension in a patient with acute stroke often is a physiologic mechanism designed to protect ischemic brain by increasing the blood flow.

Cerebral autoregulation is impaired in blood vessels irrigating that part of the brain where the stroke has occurred. Thus, blood flow to this area becomes passively dependent on arterial pressure. If the blood pressure falls, perfusion of the ischemic area declines, thereby leading to a possible increase of the infarct and jeopardizing recovery. Decreased flow also may encourage further thrombus formation and could cause additional narrowing in the originally affected artery.

Many physicians believe that hypertension worsens the outcome of acute cerebral infarction, perhaps by causing forced vasodilation, bleeding and cerebral edema. There is little clinical evidence to support this thesis. On the contrary, data exist to indicate that hypotension during an acute stroke, either through medication or from other mechanisms, may worsen rather than improve the clinical outcome by extending the original infarct and impairing flow through the watershed area.

There is some uncertainty as to the specific indications for treating hypertension in patients with acute stroke. Some experts feel that blood pressures elevated to levels of 220/130 mm of mercury or more always should be treated. Most experts recommend that therapy for high blood pressure is essential in the face of myocardial insufficiency (especially congestive heart failure), severe renal damage, retinal bleeding and when hypertensive encephalopathy clearly is present. Hypertensive encephalopathy, a term coined by Oppenheimer and Fishberg in 1928 for recurrent seizures in patients with acute nephritis with elevated blood pressure, is uncommon, is probably due to a breakdown of cerebral autoregulation and is characterized by weakness, apathy, headaches, drowsiness, seizures, visual loss, transient and often fluctuating focal neurologic signs plus coma.

As regards subarachnoid hemorrhage, many authorities now believe that induced hypertension along with volume expansion is useful to counter vasospasm. There is no clear-cut evidence that reducing the blood pressure in patients with hypertensive intracerebral hemorrhage is or is not helpful, and some literature indicates that a high blood pressure should not be lowered in this situation.

The above discussion relates only to acute stroke. The fact that chronic hypertension is the most common and potent risk factor for cerebral infarction remains undisputed. There also is good evidence that treating hypertension reduces the occurrence of stroke, and there are strong indications in the literature that lowering blood pressure after a cerebral infarction reduces the risk for subsequent events.

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Panic Disorder

ONE OF THE more interesting and rapidly changing neuropsychiatric conditions involves a heterogeneous group of disorders currently subsumed under the general heading "Panic Disorder." Although defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (DSM III), as "agoraphobia, with or without panic attacks," many clinicians find this classification inadequate. It is anticipated that the revised edition of DSM III (DSM III-R) will be a more useful reference. This topic was reviewed in the March 1983 issue of this journal and interested readers are referred to it.

Symptoms have been described as being due to a "profound activation of the sympathetic nervous system." They are primarily cardiovascular and respiratory in nature: dyspnea, palpitations, chest pain or discomfort, choking or smothering sensations, or a more general reflection of autonomic nervous system dysfunction—that is, dizziness; feelings of unreality; paresthesias in hands or feet; hot and cold flashes; sweating; faintness; trembling or shaking; fear of dying, "going crazy" or doing something uncontrolled during an attack, or a sense of apprehension or impending doom. While usually lasting for only minutes, they may persist for hours. The symptoms are accompanied by varying degrees of

nervousness and apprehension between attacks. As one might readily predict, afflicted patients may initially be seen by any of a group of specialists—a cardiologist, neurologist, gastroenterologist, internist or an emergency department physician. As more detailed physical examinations usually reveal little, the patient is reassured and told not to worry. After several episodes similar to this, both physician and patient feel frustrated, the patient often feeling abused and angry and sometimes even frightened. The idea of seeing a psychiatrist (sort of a medical "court of last resort") may be brought up—an often serendipitous choice.

Further clinical evaluation often reveals that, while initial anxiety attacks may have been spontaneous, most patients quickly discover those situations most likely to induce symptoms and begin to structure their lives to minimize their occurrence. Often, elaborate "hierarchies" of "safe" and "not-safe" activities and places are the result, leading to greatly disrupted family and personal lives.

Biologic factors are becoming increasingly important. Although data are often minimal and inconsistent, the following trends have appeared:

- Cross-cultural prevalence is between 1% and 4%, with women twice as likely to be afflicted as men.
- There is a higher concordance rate in monozygotic twins than in dizygotic twins and nontwin siblings.
- Patients with panic disorder are at increased risk for a depressive disorder.
- There is a higher rate of alcoholism, panic disorder and depression in probands of patients with this disorder.
- There is a uniform, unimodal age of onset distribution in the early 20s among afflicted patients.
- Abnormal sleep patterns, atypical responses to sleep deprivation, blunted growth hormone response to administration of clonidine hydrochloride and blunted thyroid-stimulating hormone and prolactin responses to thyrotropin-releasing hormone have been documented.
- Mitral valve prolapse occurs in up to 50% of patients with panic disorder. As many patients are also tall, thin, with long arms and narrow anteroposterior chest diameters, a systemic disorder marked by skeletal abnormalities, mitral valve prolapse and autonomic nervous system dysfunction has been postulated.
- About 80% of these patients have a panic attack when given a lactate infusion test as compared with only moderate and transient symptoms in a much smaller percentage of normal persons.
- Both the locus ceruleus and the left parahippocampal gyrus (the latter by positron emission tomography) have been found to be abnormal in many patients with panic attacks.

Treatment for the condition is divided into several types—each with its strong proponents ranging from an almost purely in vivo behavioral desensitization program to a more classical psychodynamic approach. Of the medications used, the tricyclic antidepressant imipramine, the new second-generation azolobenzodiazepine, alprazolam, and the monoamine-oxidase inhibitor phenelzine are the mainstays. A middle-of-the-road therapeutic approach involves these medications, together with behavioral exposure and cognitive and supportive psychological adjuncts. While 90% to 95% of patients are successfully treated, relapse rates range from 30% to 75%. Several courses of treatment are often necessary.

In conclusion, while theories of causation have been suggested along biologic and psychological lines, none are wholly consistent with the findings regarding the phenomenology and evolution of panic disorder. It would be premature to conclude that any unitary conceptual framework has yet been provided, and the biologic, psychological and behavioral aspects of this disorder should all receive due attention both in clinical management and scientific investigation.

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Current Concepts—Alcohol and Brain Damage

For many years central nervous system dysfunction associated with chronic alcoholism was attributed to trauma, infection, liver disease and, especially, nutritional deficiency rather than to a direct toxic effect of alcohol. The Wernicke-Korsakoff syndrome, a serious and well-known complication of long-standing alcohol ingestion, was blamed on thiamine deficiency. The average alcoholic person was felt not at risk for cerebral damage if nutrition was maintained. Newer data from animal studies, neuropsychological tests and computed tomography suggest that alcohol indeed is directly injurious to the central nervous system regardless of food intake.

There is evidence that in 50% or more of those with chronic alcoholism, cognitive changes develop that are characterized by a radiologically demonstrable, probably reversible, cortical atrophy and specific neuropsychological deficits. Among the neuropsychological deficits are a progressive disinterest in the environment, carelessness about personal appearance, impaired judgment, defective intention, slowness of thought and, on specific testing, visuoperceptive and problem-solving abnormalities. This condition, termed alcoholic dementia, is attributed to the direct effects of alcohol on the association cortex, occurs even with good nutrition and is said to depend on the duration, amount and frequency of ethanol consumption. These patients usually have a mild but not readily apparent memory loss.

In contrast, those with the Korsakoff syndrome have an anterograde amnesia manifested by interference with the transfer of information from short- to long-term memory and also a retrograde amnesia with impaired retrieval of stored information. The latter has a temporal gradient with more difficulty in recalling events close to the onset of illness than those of a more remote nature. These patients usually have relatively intact intelligence by a standard IQ test, although their memory quotient is defective. They also share the specific neuropsychological deficits of the type noted above in alcoholic dementia.

Thus, little doubt now exists that most persons with chronic alcoholism have cognitive deficits that often are mild and detectable only through relatively advanced testing. These losses appear to be of cortical origin, can be accompanied by reversible cortical atrophy and seem unrelated to nutrition. On the other hand, Korsakoff's syndrome is a se-

rious, usually irreversible amnesia of rapid rather than slow onset that is readily apparent even to inexperienced observers. This disorder seems associated in most cases with thiamine deficiency although there is some controversy at present as to the exact relationship.

The anatomic basis for the amnesia of Korsakoff's syndrome remains controversial. Recently the nucleus basalis of Meynert has been suggested as the major site of involvement. Patients with amnesia of the Korsakoff type have considerable neuronal loss in this nucleus, less than in Alzheimer's disease but more than in Huntington's chorea, in schizophrenia or in chronic alcoholism with intact memory. Currently, evidence is insufficient to definitely implicate a cholinergic basis for the Korsakoff syndrome, but further investigation of this possibility appears warranted.

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Neurologic Use of Calcium Channel Blocking Agents

CALCIUM ANTAGONISTS are now widely used for treatment of vasospastic angina, cardiac arrhythmias and hypertension. By preventing the influx of calcium into vascular smooth muscle, these agents inhibit vasoconstriction and promote vasodilation. Furthermore, in a patient with ischemia, blockage of membrane calcium channels may prevent the intracellular biochemical changes that result in infarction. Such properties have naturally led to investigation of these agents for their use in neurologic disease involving pathologic alteration of cerebral blood flow.

Migraine

Although the precise pathophysiologic mechanism underlying migraine remains unknown, a vasoactive component appears to be prominent in many patients with this disorder. Blocking migrainous intracranial and extracranial vasoconstriction theoretically may alleviate or prevent pain and reduce the incidence of associated focal neurologic deficit. Verapamil has been successfully used for migraine prophylaxis, generally in doses ranging from 40 to 80 mg three or four times a day and rarely with significant side effects; constipation and light-headedness are occasionally encountered. Nimodipine, a calcium antagonist with an apparent predilection for the cerebral vasculature, has likewise been used safely and effectively for migraine in a dose of 40 mg three times a day.

Vasospasm

Delayed cerebral vasospasm and consequent ischemic infarction are common and much-feared subacute complications of aneurysmal subarachnoid hemorrhage. Clinical experience with the calcium antagonists in this setting is limited, and there is no clear indication for their use at the present time. In one study, although the incidence of symptomatic cerebral vasospasm was not reduced by prophylactic use of nimodipine, such treatment did appear to lessen the severity of consequent neurologic deficit.

Ischemic Stroke

Pharmacologic protection against calcium-induced ischemic cell damage is a theoretically attractive therapy for acute stroke. In various experimental models of ischemic stroke, however, calcium antagonists have been inconsistently effective in reducing infarct size and may adversely influence outcome by promoting edema formation. A large-scale clinical trial of nimodipine for ischemic stroke is due to begin later this year, and, until results are forthcoming, this therapy should be considered experimental.

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Editorials

Graduate Medical Education

THE ARTICLE by Gerbert and co-workers appearing elsewhere in this issue describes the complex relationships (or lack of them) that have developed among the several organizations and agencies that have responsibilities for graduate medical education. It is a complicated system that altogether has worked quite well. It is now, however, becoming seriously stressed for many reasons. It is evident that there are already too many physicians in practice, with yet too many more in the educational pipeline who will enter practice in the next decade. A major focus of graduate medical education is on specialty and subspecialty training that may more nearly reflect the practice needs of an academic medical center or a teaching hospital than the distribution of specialties needed in the outside world of medical practice. Then, today's fiscal constraints on hospital management (and government retrenchment on providing funds) are posing a serious economic threat to the future of graduate medical education. It will no longer be financed in the traditional way—that is, largely through income from private patient care. And finally, the Federal Trade Commission always keeps a wary eye on anything that smacks of organizational interference with a physician's right to practice in a specialty of his or her choosing.

All of this points to stressful times ahead for graduate medical education. One can only wonder whether the complicated graduate medical education system that has evolved over the years in the private sector will be willing or able to address these social and economic problems effectively. It is worthy of note that the Department of Health and Human Services has recently appointed a Council on Graduate Medical Education to "advise the HHS Secretary and Congressional committees regarding the supply and distribution of physicians in the United States, current and future physician specialty shortages and surpluses and issues relating to foreign medical graduates." The council was also charged with making recommendations on appropriate efforts to be carried out by hospitals, medical schools and accrediting bodies, and "to encourage entities providing graduate medical education to conduct activities to voluntarily achieve the recommendations of the Council."

It is clear that there are many changes ahead for graduate medical education. It is to be hoped they will be accomplished by a collaborative effort among all the parties concerned.

MSMW

Immunotherapy—Is the Treatment Worse Than the Disease?

THERE ARE MANY interesting and provocative dilemmas in modern medicine. I recall back in the 1950s that a very common subject for magazine articles, cartoons, science-fiction novels and movies was the situation wherein a scientist had discovered a cure, but, unfortunately, nobody was really sure to what disease.

This type of theme is not new in medicine where the knowledge of complex components of human biology, health and disease tends to progress at an uneven pace, and where, from time to time, we know a greater amount about the pathogenesis of a disease than about methods to treat, cure, divert, deflect, postpone or prevent.

In this issue of the journal, Geffner and Lippe have very concisely reviewed the situation with type I (insulin-dependent) diabetes mellitus and the possible role of immunotherapy. An immense amount of new knowledge concerning early type I diabetes has been generated over the past decade, particularly related to the autoimmune defects that seem to precede the hyperglycemic stage of the disease by perhaps as long as a decade.

The genetic component (perhaps somewhere in the short arm of chromosome 6 near the human leukocyte antigen determinants) remains to be unearthed, as does what appears to be an important environmental triggering factor for genetically susceptible persons. Information available tomorrow may render quite viable some type of genetic testing for those with prehyperglycemic insulin-dependent diabetes. In addition, the next mail may bring a journal with exciting information that the environmental agent has been identified and one can very easily and cheaply eliminate it or produce a vaccine for it. Nevertheless, the best we have today are measures and tests for the autoimmune components.

Further reflection, however, does suggest caution in planning type 1 diabetes prevention. The theory of the apparent homogeneity of type 1 diabetes with a neat sequence—genetic susceptibility, autoimmune defect and β-cell destruction—still has a number of serious flaws.

As nicely reviewed for us by Geffner and Lippe, the differences between current animal models of type 1 diabetes and the human model do create a few annoying problems. The BB/W rat has been immensely useful, but there are some dissimilarities not yet explained, such as the fact that they are hyperglucagonemic and have a number of immunologic differences compared with type 1 human diabetes. The puzzling lymphopenia may be providing an unrecognized but important message related to the suitability of such a model on which to base intervention programs in humans. A confusing difference in diabetes sex prevalence, particularly in the nonobese diabetic mouse, has not been adequately explained. Importantly, there are really not good parallelisms between the assays of the defect in autoimmunity in rat-mouse models versus humans and only very sketchy data on the sequence of events that take place at the level of β-cell function in these animal models. Admittedly, it is difficult to do a variety of oral and intravenous perturbations in such tiny models, but I, for one, would like to see much more data published than are now available. I suspect the central and most important feature is the universal measured defect in humans just before type 1 diabetes mellitus of the loss of early-phase insulin release after intravenous administration of glucose.

Obviously, the information that has been accumulating has been exciting and has clearly justified carefully conducted, well-supervised immunotherapy trials. Using immunotherapy in subjects in whom only 1% of insulin secretion remains is a situation in which, at best, the interpretation of results will be difficult. Even if one quadrupled the β-cell function after a reasonably short course of immunotherapy, if one started with only 1% of normal β-cell function, it would be difficult to quantify a significant increase. Physiologic variations, assay variability and so forth make such small insulin increments difficult to measure. It becomes clear that a human population for such trials has to be made up of individ-

uals with a lesser degree of β-cell failure, those who do not have type I diabetes but true pre-type I diabetes.

It will be hard to define the risk-benefit ratio in such "normoglycemic yet insulinopenic" populations, considering the spectrum of potent immunosuppressant drugs currently available. Critical questions relate to administering these agents to young children, determining the period of time that the agent must be used and, even more importantly, defining tests that are specific and sensitive enough to indicate the lack of progress of the immunodefect and β-cell function or reduction of the autoimmune defect and the reversal of the impaired insulin secretion.

Another crucial issue is the design of such studies. Without having sufficient information concerning the natural history of all of the features of type I diabetes, appropriate experimental design and subject inclusion criteria are difficult to establish.

A controlled randomized study design is obviously one that has to be given serious thought. This raises the spectre of an expensive, complex, multicenter clinical trial, but considering the importance of the possibility of postponing or preventing type I diabetes, this could be an issue that deserves considerable support.

The language, semantics and definitions that have to be used in communicating thoughts, ideas, plans and progress may also need refinement. Some of the words that bother me are "remission," "control," "insulin-dependent" and "β-cell function."

The establishment and encouragement of ongoing workshops and comparison groups related to assays used in assessing immunotherapy have been and will continue to be an important component in handling this difficult problem. The superimposition of some type of a clearinghouse mechanism to improve this networking would be gratefully received by all workers in the field.

Finally, this is now a key and crucial time for the type I diabetic constituency to play their role and to make their mark. High-risk groups—those with diabetes multiplex, monozygotic twins discordant for type I diabetes mellitus, first-degree relatives of type I diabetics—should be encouraged to learn more about what their contributions to this effort might be. The health agencies such as the American Diabetes Association, local diabetes societies, the Juvenile Diabetes Foundation and the like should educate to ensure that the diabetic constituency (and the direct benefactors of such clinical research) could play an informed and enlightened role as true collaborators. "Let the people be heard."

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Is the Dollar Mentality in Health Care Healthy?

THE DOLLARS in health care are important. There is no gainsaying this. But are the dollars what health care is really all about? Is it actually healthy to shift health care dollars away from what appear to be excessive costs toward profits that benefit institutions and persons that may only have a dollar incentive to provide the health care that is needed? One senses that somehow something is wrong and that somehow this is not healthy. There is already reason to believe that the present preoccupation with dollar costs and dollar profits, with only relatively superficial lip service to the access and quality of services that are needed by many, may be seriously croding what health care is all about. It seems almost to go without saying that health care should especially be for those who need it most. And this could be any of us.

The "dollar mentality" in today's health care focuses on dollars, not people. Cost conscious governments, national, state and even local, are de facto no longer able to cope, and are withdrawing needed care for the indigent sick, not to mention the homeless, because of the dollar costs. Private enterprise, whether in business or industry or health care, also needs to keep costs down. Even hospitals are moving the "bottom line" further up on their lists of purposes and priorities, no doubt influenced if not impelled by the government imposed system of DRG payments for services to Medicare patients. And, even of greater concern, more and more physicians and other health professionals are developing, often of necessity, a similar dollar mentality with respect to where and how they will conduct their practices.

How can all this be healthy for health care? If it is true, as some are beginning to believe, that the only goal of health care is simply someone's financial gain or profit, then yes, all of this is healthy for the health care system. But there are many, and this author hopes that we are in a majority, who believe that the health care system is less for profit than for adequate access and quality of care for those who need its services—that is, the sick, injured and emotionally disturbed—as well as to promote the health and well being of those who are not yet sick. What then is the relationship between a financially healthy health care system and a system that provides adequate health care services for all those who need them? This would seem to be the nut of a great big problem.

In the real world of economics it is unlikely that it will ever be found financially profitable to care for the very ill, those who cannot pay, the homeless, the underfed or any of the disadvantaged. Indeed governments, business, industry, hospitals and even health care providers have found this to be true, or soon will. The fact is, that in the present health care environment, it is simply not in the cards for a profit oriented health care system to provide adequate care where the need is greatest. And it is also true that in the long run it cannot be in the social, economic or political interest of the nation as a whole to allow the dollar mentality in health care to go so far as to displace the real purpose of our health care system. The answers will not be easy, but they must be found before we sacrifice what health care is all about to this dollar mentality that now seems to prevail so widely with respect to health care in this nation.

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Case Reports

Recurrent Hemoptysis Treated by Bronchial Artery Embolization

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In most patients with significant recurrent hemoptysis, clinical or radiographic evaluation will show an abnormality. Assessment of these patients should include exclusion of systemic bleeding abnormalities, chest radiography, bronchoscopy, thoracic computed tomography (CT) and bronchography.[1-7] If these studies are normal, bronchial angiography should be considered for a small vascular lesion of the lung.[1-5] Vascular abnormalities are an uncommon cause of recurrent hemoptysis, but a number of cases have been reported.[2-5,6] Bronchial angiography is diagnostic and may lead to appropriate curative procedures, such as bronchial artery embolization.[6-12]

We report the case of a patient with recurrent severe hemoptysis and normal radiographic studies who had a hypervascular lesion of the right hilum on bronchial angiograms. This was treated by bronchial artery embolization with complete resolution of symptoms.

Report of a Case

The patient, a 36-year-old woman, was referred because of multiple episodes of hemoptysis that began 15 months earlier and were unassociated with predisposing factors. The initial episode consisted of about 100 ml of blood daily for several days and then subsided spontaneously. This recurred seven, five and three months before admission. Chest radiographs were normal except for left-sided patchy consolidation that was seen after an episode of hemoptysis, cleared over two days and most likely represented aspirated blood. A thoracic CT scan, bronchograms and results of a systemic evaluation including clotting studies were normal. Bronchoscopy showed blood from the right lung but no source of the bleeding. Her past medical history and physical examination elicited no abnormalities. There were no skin or mucous membrane telangiectases.

Because the risks of recurrent hemoptysis include life-threatening hemorrhage and the anxiety caused by these episodes, bronchial angiograms were done to detect a vascular lesion. The arteriograms showed an enlarged right bronchial artery supplying an extensive network of abnormal vessels in the right hilum. These vessels were characterized by focal areas of narrowing and dilation and lack of normal branching (Figure 1).

The anterior spinal artery did not arise from the right bronchial artery (Figure 1). The proximal right bronchial artery was embolized with 0.25 mm particles of polyvinyl alcohol. A subsequent angiogram showed almost complete occlusion of the bronchial artery at the origin of the previously noted vascular abnormality (Figure 2). The procedure was without complications.

The patient has now been observed for nine months without recurrence of her hemoptysis.

Discussion

Bronchial angiography may be of value in the workup of patients with recurrent hemoptysis in whom common disorders, such as bronchitis, tumors, infection, tuberculous cavitation or bronchiectasis, have been excluded. It can show tumor vascularity, systemic to pulmonary shunts or shunts to the systemic veins. In rare cases when a patient is actively bleeding, the bleeding site itself may be visualized.[6-12] Angiography is often useful in patients with hemoptysis of known cause, as treatment by embolization may be done.[6-12]

We have seen one other patient with a vascular lesion of the right lower lobe who presented with hemoptysis. CT in this patient showed a vague, increased density in the right lower lobe. On a bronchial angiogram, there was diffuse abnormal vascularity and systemic-pulmonary venous shunting (Figure 3). The lesion was resected and shown to be a pulmonary hemangioma supplied by the bronchial artery.

The finding of abnormal vessels during bronchial angiography in the absence of abnormalities on chest radiographs is uncommon. Three cases of patients with hypervascularization on bronchial angiograms with normal chest radiographs, bronchograms and bronchoscopy have been reported.[5] The appearances in these three were similar to those in our two patients. In a series of 122 cases of bronchial angiography for benign pulmonary disease, five cases were of undiagnosed cause, three of which presented with hemoptysis.[3] Of these

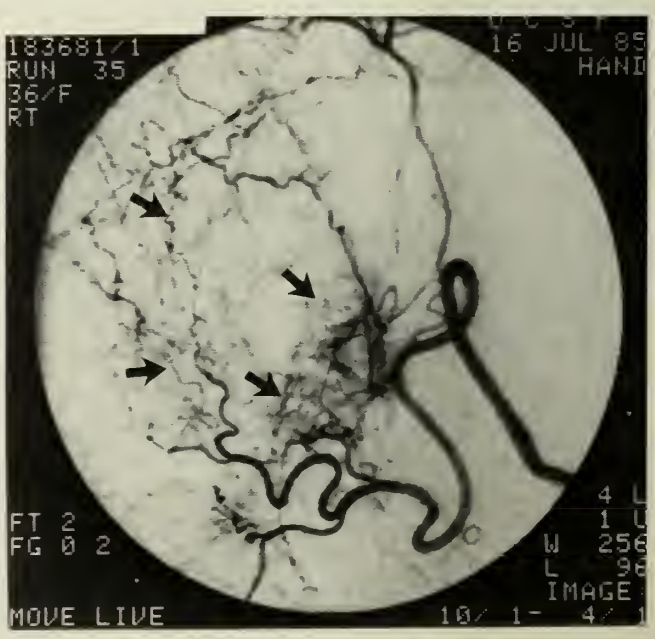

Figure 1.—A right bronchial artery digital subtraction angiogram shows the central vessel to be enlarged. A tangle of abnormal vessels (arrows) is seen arising in the region of the hilum and right main stem bronchus. No early-filling veins or pulmonary artery shunting is seen.

(Stein MG, Stulbarg MS, Webb WR, et al: Recurrent hemoptysis treated by bronchial artery embolization. West J Med 1987 Mar; 146:358-359)

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three patients, two had increased bronchial artery vascularity, and the presence of hemoptysis was related directly to the degree of bronchial hypervascularity. In another series, Rémy and co-workers had one patient with hemoptysis—categorized as undiagnosed—treated successfully with embolization.[6] Viamonte and associates showed that normal bronchi may have increased vascularity associated with hemoptysis.[2] They described this appearance as hypervascularity, analogous to the findings in our patient.

Bronchial artery embolization is well documented for patients with massive as well as recurrent hemoptysis not amenable to resection.[6-11] In a recent series of 29 patients with repeated hemoptysis, 11 (38%) had a good long-term result. All these patients, however, had an obvious cause of hemoptysis, such as cystic fibrosis, tumor or infection.

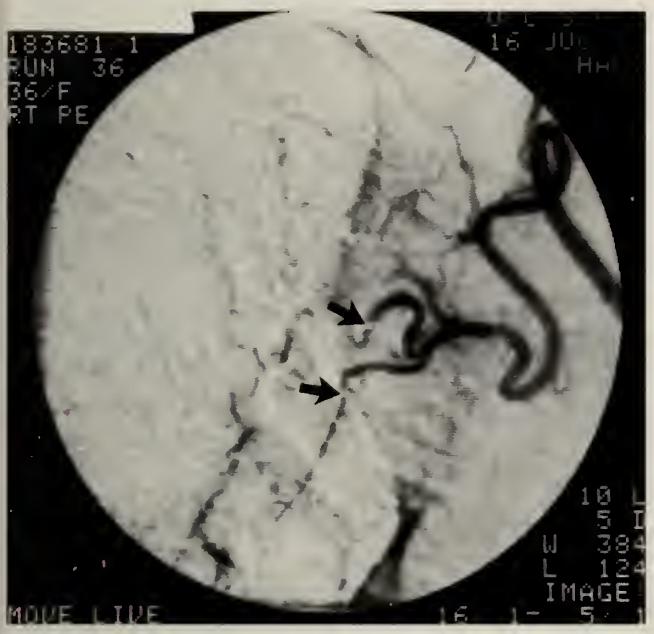

Figure 2.—A digital subtraction angiogram done after embolization of the right bronchial artery shows intraluminal filling defects from the polyvinyl alcohol **(arrows)**. The previously seen abnormal vessels (Figure 1) are not visualized.

Figure 3.—A right bronchial angiogram from another patient with hemoptysis shows an abnormal collection of vessels **(arrows)** in the right lower lobe that filled off the bronchial artery. An early draining vein **(open arrow)** is seen, which pathologically was a pulmonary hemangioma.

Complications of bronchial angiography are unusual. The most common include substernal chest pain, fever, dysphagia, convulsions and peripheral embolization (due to reflux of the embolizing material into the aorta). Embolization of the anterior spinal artery with spinal cord infarction is very rare. Care should be taken, however, to place the catheter tip distal to the origin of this vessel.[6-11] Bronchial angiography is suggested in assessing a case of recurrent hemoptysis when a source cannot be found by CT, bronchography and bronchoscopy. When an area of hypervascularity is shown, bronchial embolization could be considered.

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Wegener's Granulomatosis Presenting as Vertigo

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WEGENER'S GRANULOMATOSIS is an unusual disease characterized by necrotizing granulomas and vasculitis of small arteries and veins. Its classical involvement of the upper and lower respiratory tract and kidneys is well recognized.[1] It has more recently become apparent that Wegener's granulomatosis can exist in a localized form involving only the upper respiratory tract,[2] though multiorgan system involvement is the rule.[3,4] Otologic involvement in Wegener's granulomatosis occurs in about 20% of cases and usually presents with symptoms referable to impaired auditory function. Herein we

(Bennett RW, Staker LV: Wegener's granulomatosis presenting as vertigo. West J Med 1987 Mar; 146:359-361)

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report an unusual case of histologically confirmed Wegener's granulomatosis with otologic involvement in which the initial symptom of disease was vertigo.

Report of a Case

The patient, a 74-year-old woman, had positional vertigo seven months before a diagnosis was made. She complained of a "whirling" sensation that was exacerbated by head turning. She said she did not have tinnitus or vomiting. A month later she noted the onset of a sensation of dryness and stuffiness of her nose, associated with a decrease in auditory acuity. She consulted a physician who treated "fluid in the inner ear" with a 30-day trial of furosemide (Lasix) administration without benefit. A 30% bilateral hearing loss was documented by audiogram. A month before presentation a repeat audiogram showed an additional 5% to 10% bilateral hearing loss and a dry, nonproductive cough developed; vertigo persisted and a trial of low-dose prednisone (5 mg) was given, without improvement.

An ear, nose and throat evaluation showed bilateral serous otitis media. A course of co-trimoxazole (Septra) given orally and beclomethasone dipropionate inhaled nasally gave no relief. Despite the placement of bilateral tympanostomies, her symptoms, including vertigo, persisted.

On presentation she was noted to have mild hoarseness due to a chronic cough. Examination of her head, eyes, ears, nose and throat showed five beats of horizontal nystagmus with no positional component. Bilateral tympanostomy tubes were in place. The remainder of her examination elicited no abnormalities. On laboratory evaluation a Westergren sedimentation rate was 47 mm per hour and analysis of urine showed microscopic hematuria with an occasional erythrocyte cast. A chest x-ray film showed ill-defined infiltrates in both apices. Sinus films were normal. A subsequent open-lung biopsy specimen (Figure 1) showed granulomatous vasculitis, and a diagnosis of Wegener's granulomatosis was made.

The patient was placed on a regimen of cyclophosphamide, prednisone and co-trimoxazole, and her symptoms of cough, vertigo and hypoacusis promptly resolved. Follow-up audiograms revealed slight improvement (Figure 2).

Discussion

As reviewed by Bradley,[5] Wegener's granulomatosis involves the ear in three well-recognized and distinct forms: (1)

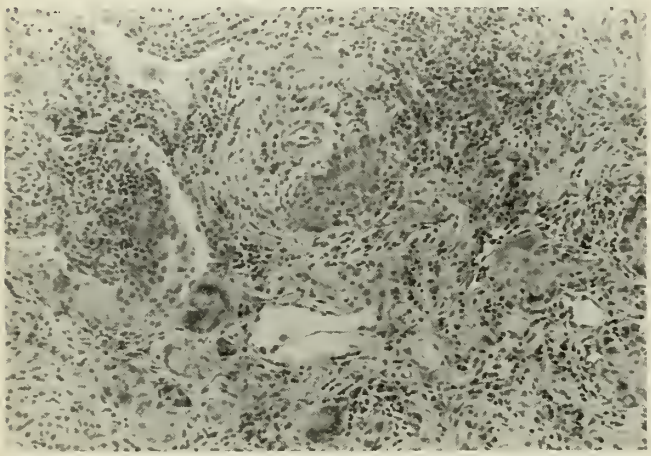

Figure 1.—A lung biopsy specimen shows perivascular, granulomatous, inflammatory infiltrate consistent with Wegener's granulomatosis (hematoxylin and eosin stain, original magnification × 50).

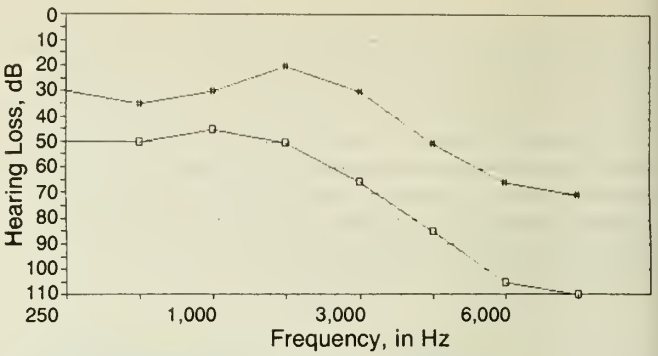

Figure 2.—Sequential audiograms show objective auditory improvement in response to therapy. □ = before therapy, # = at 4 months' follow-up

serous otitis media, either unilateral or bilateral; (2) destruction of the middle ear and mastoid due to actual involvement with Wegener's granulomatosis, and (3) a sensorineural deficit, usually in association with a conductive hearing loss. McCaffrey and co-workers describe the cases of 21 patients with otologic involvement in Wegener's granulomatosis[6]; of these, 5 had chronic otitis media, 19 had either unilateral or bilateral serous otitis media, and 9 (43%) had a sensorineural hearing loss. They go on to mention only one patient with vertigo as a complication of disease.

It is intriguing to consider why there is such a high incidence of sensorineural hearing loss, but apparently very infrequent, clinically recognizable vestibular involvement as manifested by vertigo. Leone and associates report on one patient with Wegener's granulomatosis and sensorineural hearing loss whose autopsy surprisingly showed a thickening of vessels adjacent to the endolymphatic sac, with otherwise normal-appearing cochlear vessels.[7] As discussed by Cairns and colleagues, immune complexes in Wegener's granulomatosis seem to play a role in the activity of disease.[8] Leone and co-workers contended that immune complex deposition in the fenestrated capillaries of the endolymphatic sac induced consequent alterations in the composition of the endolymph, thus altering the cochlear microenvironment and inducing hearing loss. Why, then, would the vestibular apparatus not be similarly affected? The implication is that the cochlear portion of the labyrinth is more susceptible than the vestibular portion to the consequences of this vasculitis. Other explanations for the sensorineural hearing loss include granulomatous compression on the cochlear nerve or vasculitis involving the cochlear vessels, neither of which were confirmed by Leone and associates. Clearly there is a need for further histologic investigation into the cause of sensorineural hearing loss and vertigo in this disease.

This patient's symptoms may have been a manifestation of vasculitis involving the entire vestibulocochlear nerve. Central nervous system involvement has been reported in approximately 10% of patients with Wegener's granulomatosis.[3] It assumes multiple forms, including cranial nerve deficits and mononeuritis simplex or multiplex. This still, however, does not explain the disparity between the incidence of vestibular and cochlear symptoms in the more usual forms of otologic involvement.

Whatever the cause for this disparity, it seems clear that Wegener's granulomatosis continues to be an intriguing disorder. Otologic involvement is frequent in the form of cochlear disease, but vestibular involvement manifested by vertigo

is a distinctly unusual presentation and should be remembered when assessing elderly patients with vertigo.

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Refractory Scleritis Due to Wegener's Granulomatosis

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WEGENER'S GRANULOMATOSIS is a systemic disease associated with necrotizing granulomas and vasculitis.[1] The triad of sinus, lung and renal involvement is frequently described, but the vasculitis may affect many organs. The incidence of organ system involvement, in decreasing frequency, is lungs (94%), sinuses (91%), kidneys (85%), joints (67%), nasopharynx (64%), ears (61%) and eyes (58%), with skin, nervous system, heart and other organ systems being involved less frequently.[2] A limited form of Wegener's granulomatosis without renal disease tends to have a less serious course.[3] Mean survival has increased from 5 months without treatment to 12 months with prednisone therapy and to more than 5 years with the addition of cyclophosphamide.[1] We report the course of an unusual case of Wegener's granulomatosis with severe scleritis that remained refractory to all forms of therapy and led to blindness in one eye.

Report of a Case

The patient, a 67-year-old woman, had a diagnosis of Wegener's granulomatosis made in 1978 by open lung biopsy. Over a period of two years previous to this time, she had had mastoiditis, polyarthralgias, nasolacrimal duct obstruction and a diffuse scleritis of the right eye that took about four months to control. At the time of diagnosis she had pulmonary infiltrates, sinusitis and mastoiditis. She has never had renal involvement. She had prompt remission with a regimen of cyclophosphamide in which the doses were tapered over 1½ years. After being off therapy for more than two years, recurrent sinus disease developed, together with new lung infiltrates and a painful nodular scleritis of the left eye. Sinus and lung involvement cleared quickly on a regimen of cyclophosphamide, 100 mg a day, but the scleritis persisted. Because of progressive eye involvement, prednisone therapy (60 mg a day) was added, and this was maintained in varying amounts over the next nine months without improvement.

Figure 1.—Resolving nodular scleritis with staphyloma superotemporal to the limbus just before surgical treatment for cataract and glaucoma. The posterior synechiae are due to uveitis.

In June 1985, her vision was 20/25 and 20/40 in the right and left eyes, respectively. Evidence of quiet, old scleritis was noted in the right eye. In the left eye a large, tender, limbal nodule measuring 7 mm by 7 mm and elevated 2 mm was noted superotemporally. Areas of thinning were present. There was a 2+ cell-and-flare reaction in the anterior chamber with three posterior synechiae noted. The intraocular pressures were controlled with medication. There was no evidence of proptosis or orbital disease. She was being treated with cyclophosphamide (Cytoxan), 50 mg twice a day, for more than a year; prednisone, 40 mg a day; acetazolamide (Diamox); prednisolone acetate (Pred Forte) every three hours, and cycloplegic drops topically.

Despite no obvious systemic activity, the eye progressively deteriorated. Because of this she was given pulse therapy of intravenously administered cyclophosphamide, 1 gram every two weeks, and methylprednisolone sodium succinate (Solu-Medrol), 1 gram every two weeks, for four doses to see if this would have any effect on the eye disease. Because none of this produced any change in her eye disease and because she had had no other systemic symptoms for a year and a half, the doses of cyclophosphamide and prednisone were tapered off.

In November 1985, her vision had dropped to 20/70 in the left eye, and she was still experiencing constant pain and tenderness. Several short-acting subconjunctival steroid injections (dexamethasone [Decadron], 2 mg) near but not immediately adjacent to the area of scleritis had failed to have any effect. The nodule was larger and thinner. The uveitis was more severe with almost 360-degree posterior synechiae, and cataract development was well advanced (Figure 1). Shortly thereafter, she had a pulmonary relapse that again responded to a regimen of cyclophosphamide and prednisone.

(Hodges EJ, Turner S, Doud RB: Refractory scleritis due to Wegener's granulomatosis. West J Med 1987 Mar; 146:361-363)

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In January 1986, her vision was down to 20/200 with persistent sclerouveitis and uncontrolled glaucoma. In addition, systemic intolerance had developed to the prednisone therapy, with proximal muscle myopathy and hypertension. Because of this, cyclosporine, 10 mg per kg body weight, was added to her regimen. After one week of therapy, she had pronounced intolerance, manifested by weakness, nausea, fluid retention, confusion and gingival ulcers, and she refused further systemic or topical administration of cyclosporine.

During the entire course of her disease, the leukocyte, erythrocyte and platelet counts have remained within normal limits, apart from the acute exacerbations of disease. She has not required alteration of the dosage of cyclophosphamide on account of marrow suppression. Serum levels of bilirubin, alkaline phosphatase and aspartate and alanine aminotransferases have all remained normal, even during the period of intolerance to cyclosporine therapy. Her serum creatinine level has always remained normal, although there have been fluctuations in the blood urea nitrogen level.

She has subsequently had a successful filtering procedure for glaucoma and cataract extraction. A periosteal support graft for the area of scleral thinning is planned. The scleritis is gradually resolving after three years, and she will remain on a regimen of cyclophosphamide for at least another year.

The loss of vision in this woman originally was due to the development of a posterior subcapsular cataract secondary to uveitis and the use of steroids. Visibility was not clear enough during fluorescein angiography to detect any possible added visual compromise due to inflammation-induced macular edema. In time the inflammatory changes produced peripheral anterior and posterior synechiae and medically uncontrollable glaucoma. The cataract and glaucoma operations were uncomplicated without any further rise in intraocular pressure. When the disc could again be seen, there was optic disc atrophy with a 0.9 cup:disc ratio due to the sustained elevation of intraocular pressure. This was an expected possibility but could not be known for sure as the very dense cataract obscured visualization and the posterior synechiae and cycloplegia interfered with assessment of the efferent arc of the pupillary light reflex.

Comment

Reports of ocular involvement in Wegener's granulomatosis vary widely but generally it is reported to occur in from 30% to 50% of cases.[1,4-6] The most common ophthalmic findings include orbital inflammation, corneal or scleral involvement and episcleritis.[6] Scleritis and ulcerative keratitis each may occur singly or as contiguous lesions, with postinflammatory thinning of tissue frequently occurring. Externally the eyelid (ptosis and edema due to orbital disease) and nasolacrimal duct are less often involved. Intraocular manifestations include uveitis, narrowed retinal arterioles, cotton-wool spots and retinal hemorrhages, all in the absence of hypertension. Optic nerve inflammation and compression from orbital lesions also occur less commonly. Loss of vision may occur from corneal scarring (exposure, postinflammatory scarring), the complications of uveitis (macular edema, glaucoma, cataract) and retinal and optic nerve involvement.

Often one is left with maintaining an index of suspicion and making a diagnosis when other more obvious features appear. The disease has often been noted to present with ocular involvement, and in one report ocular symptoms occurred 15 years before a diagnosis could be established.[7] If a diagnosis has not yet been made, it is dangerous and usually noncontributory to take a scleral biopsy, so unless there are other concurrent lesions that are diagnostic, treatment can only be symptomatic, with the realization that other areas of involvement may occur later in the evolution of the disease, allowing a more specific treatment regimen.

In this case, remission was always readily induced with cyclophosphamide alone or in combination with prednisone. All evidence of systemic disease subsided on several occasions, except for the painful scleral disease that continued to smoulder and remain unresponsive to medical intervention for more than three years despite high and prolonged doses of immunosuppressive therapy. A partial explanation may be poor drug delivery to the sclera due to vasculitis and also because the sclera itself is poorly perfused. In addition, the eye symptoms may seem disproportionately severe due to the delicate nature of the ocular tissues involved, which may cause pain and visual loss very early in the course of inflammation. Due to the location of this lesion, this patient did go on to have uveitis, cataract, staphylomatous scleral thinning and severe, painful glaucoma due to the scleritis.

Although administering cyclosporine has been reported to be successful in cases of ocular Wegener's granulomatosis unresponsive to conventional therapy,[8] our patient had severe side effects and was unable to have a satisfactory trial of therapy. The severity of the side effects was unusual and was undoubtedly due to the concomitant effects of fluid retention from prednisone and the side effects of acetazolamide. Fortunately, despite intolerance to prednisone, she has exhibited none of the short- or long-term complications of cyclophosphamide therapy.

The limited form of Wegener's granulomatosis may have a better prognosis for life due to the fact that most deaths occur from renal disease; the limited form, however, does not preclude the possibility of eye disease being equally as severe as in the full-blown disease,[9] as exhibited by our patient in whom blindness in one eye developed.

This report emphasizes the need for early suspicion of the disease; the serious and persistent nature of scleral disease, even in the limited form of Wegener's disease; the lack of response to treatment of scleritis, with severe and prolonged secondary eye complications, and a possible argument for earlier surgical intervention to treat irreversible secondary complications such as glaucoma or progressive scleral thinning.

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Fatal *Strongyloides stercoralis* Infection in a Patient Receiving Corticosteroids

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Strongyloides stercoralis can persist as a subclinical infection for years, only to become manifest when host defense mechanisms become impaired.[1-5] A case of fatal *S stercoralis* infection is presented to underscore the importance of considering *Strongyloides* as a potential infection in an immunocompromised host who has lived in an endemic area.

Report of a Case

The patient, a 78-year-old Cuban man, was referred to the Los Angeles County-University of Southern California Medical Center for the treatment of severe, steroid-dependent, obstructive airways disease. The referring physician also noted that a hoarse voice, difficult deglutition and a sore throat had recently developed. There were no other gastrointestinal complaints on admission. On physical examination he had a respiratory rate of 28 per minute. An indirect laryngoscopy showed normal vocal cords. Diffuse wheezes were heard on examination of the chest.

The leukocyte count was 4,500 per μl, with 57% segmented neutrophils, 22% band forms, 12% lymphocytes and 8% eosinophils. A sputum Gram's stain showed 3+ polymorphonuclear leukocytes and 3+ Gram-negative rods. A chest x-ray film showed no abnormalities.

Because of progressive respiratory failure, an endotracheal tube was inserted and the patient was placed on mechanically assisted ventilation. Therapy with ampicillin and gentamicin sulfate was started. The patient's airways disease was managed with a regimen of hydrocortisone, aminophylline and metaproterenol sulfate. Despite vigorous therapy, the patient became comatose and hypotensive and died on the third hospital day.

On gross examination at autopsy, the pharynx was clear of lesions, but the trachea showed extensive hyperemia. The gastrointestinal tract from the stomach to the large intestine showed areas of mucosal erosion. Microscopic examination of lung tissue disclosed *Strongyloides stercoralis* organisms in large numbers, with histiocytic infiltrates surrounding the organisms (Figure 1). On microscopic examination of duodenum and jejunum, many *S stercoralis* organisms were seen in areas of necrosis (Figure 2). The esophagus was normal. The cause of death as determined by autopsy findings was disseminated *Strongyloides stercoralis* infection.

Comment

Strongyloidiasis is endemic throughout the subtropical and the tropical regions of the world. In America, the endemic area is the rural South[6]; our patient had lived in Cuba for most of his life and, presumably, had contracted the infection there. The endogenous cycle, in which filariform larvae can penetrate the gut wall or the perirectal tissue of the host, may persist for as long as 30 years[6] and may be asymptomatic in 50% of cases.[3] Impaired cell-mediated immunity can result in accelerated infection. Hosts at risk include patients receiving immunosuppressive or cytotoxic therapy. Indeed, in animal models, the administration of corticosteroids initially is associated with an absolute increase in worm count and a fractional increase in invasive filariform larvae relative to the noninvasive rhabdoid larvae.[5] Patients receiving corticosteroid therapy for diseases as varied as the nephrotic syndrome, systemic lupus erythematosus and asthma have had disseminated strongyloidiasis. To date, there have not been cases of hyperinfection with *Strongyloides* reported among patients with the acquired immunodeficiency syndrome, though given the appropriate exposure history, persons in that group would be at risk.[1]

Our patient received prednisone at daily doses ranging

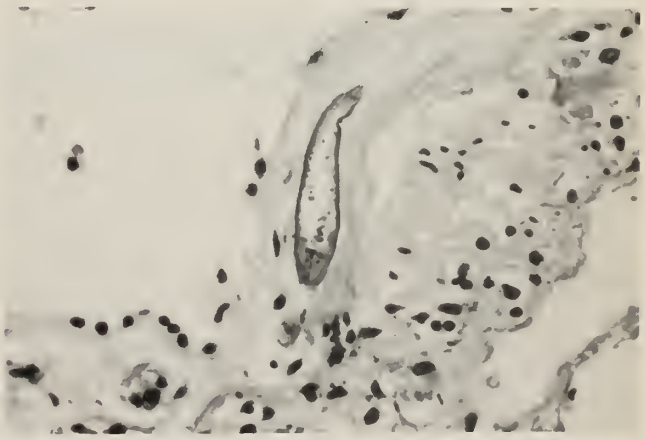

Figure 1.—A photomicrograph of lung tissue shows a filariform larva (reduced from magnification × 100).

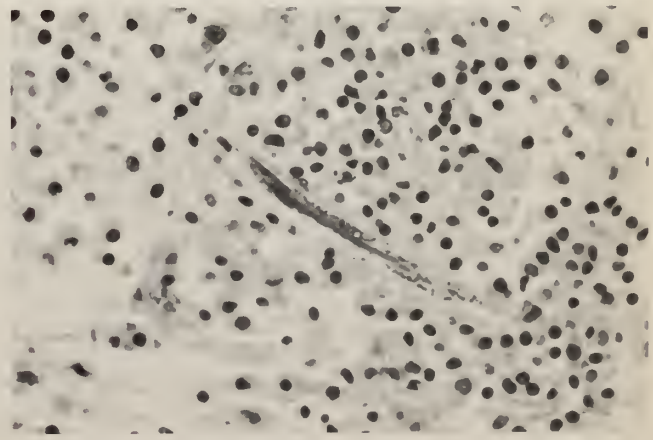

Figure 2.—A photomicrograph of duodenal tissue shows adult *Strongyloides stercoralis* in areas of necrosis (reduced from magnification × 100).

(Yee A, Boylen CT, Noguchi T, et al: Fatal *Strongyloides stercoralis* infection in a patient receiving corticosteroids for obstructive airways disease. West J Med 1987 Mar; 146:363-364)

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from 20 mg to 40 mg in the six months before admission to our service. The dissemination or accelerated endogenous cycle of the worm is responsible for the clinical findings. There can be the development of abdominal pain, emesis, diarrhea or ileus, the last of which can exacerbate the problem of increasing parasitosis by prolonging gastrointestinal transit time. Filariform larvae can then penetrate across the bowel wall in large numbers, often carrying enteric bacteria "piggyback" to distant sites.[5] Respiratory insufficiency may result from accelerated parasitic infestation. Eosinophilia, which may be seen in blood specimens during the indolent phase of infection, is generally not present during the hyperinfective, disseminated phase,[2] as was the case in our patient, whose absolute eosinophil count on admission was 360 per μl. Whether this lack of eosinophilia played a permissive role in the development of hyperinfection is not known.

Stool examinations for ova and parasites are often not adequate to achieve a diagnosis,[3] as was the case with our patient, who had loose stools develop on the second hospital day. In a case wherein an immunocompromised host who has the appropriate exposure history has gastrointestinal symptoms and wherein initial stool specimens are not diagnostic, duodenal and jejunal fluid examination, for instance by the Enterotest technique, is indicated.[5] Indeed, it should be emphasized that patients with the appropriate exposure history who have eosinophilia should have several stool specimens sent for ova and parasite studies. Should an initial three stool specimens show no ova or parasites, further diagnostic workup would depend on the clinical picture.

Examining sputum specimens for ova and parasites may also be helpful.[2] Our patient did complain about a hoarse voice, sore throat and difficulty swallowing. It is known that the larvae of *S stercoralis* do migrate into the trachea and the hypopharynx. An examination of sputum for ova and parasites might have been the diagnostic procedure of choice.

Thiabendazole is the medication to use for the treatment of strongyloidiasis. The standard dose is 25 mg per kg of body weight twice a day by mouth for two days. Where hyperinfection or dissemination develops in an immunocompromised host, the treatment is extended to seven days, using the standard dose of thiabendazole. A follow-up upper gastrointestinal tract aspirate is indicated. Immunocompromised hosts at risk for recurrent strongyloidiasis can receive monthly prophylactic treatment.[5]

In summary, hyperinfection or dissemination of *Strongyloides* should be in the differential diagnosis when an immunocompromised host with the appropriate exposure history presents with gastrointestinal and respiratory tract symptoms. Although the signs can be subtle and the diagnosis difficult to establish, treatment is available.

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Nonsurgical Treatment of Lumbar Disc Sciatica

To the Editor: I congratulate *The Western Journal of Medicine* for publishing the article on outpatient treatment of lumbar disc sciatica[1] and the authors of this article for the success in their outpatient management where 39 out of 47 patients recovered without surgical treatment and without admission to hospital.

Unfortunately the authors do not describe their method of treatment in sufficient detail to permit a duplication of their study. They only reveal the following: "The strategies for home treatment include detailed instruction in bed transfer, chair and car transfer, choice of seating, easily applied and correctly fitted lumbosacral corsets, home cold pack therapy, providing hospital beds for home and raised toilet seats when necessary." This program seems to apply the principle of maintaining a low intradiscal pressure which we published more than ten years ago.[2] Had the authors used this principle even more strictly they could have further reduced the number of surgical cases.

In their discussion the authors emphasize the relatively low cost of nonsurgical treatment compared with the very high cost of surgical treatment. This may be important. But much more important in my opinion is to point out that an adequate nonsurgical management is entirely without risk while the surgical treatment carries the risk of anesthesia, the risk of infection and the risk of possible neurologic damage. Furthermore, the end results of adequate nonsurgical management are considerably better than those of surgical management.

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On Maintaining a Professional Attitude

To the Editor: Medicare's payment policies, malpractice worries, contracting pressures, rising overhead and the like all take their toll on us out here in the real world of private practice. Is it worth it?

What's our alternative to becoming demoralized? Let's stop and think about the big picture.

Our services are "consumed" not by a nameless "customer," but usually by a sick, worried person looking for some sincere help. And the traditional personal, private physician has the most incentive to provide this humane care. But employers, insurance companies and patients aren't very loyal when they think they can save money (although they are now learning the lessons of "bargain basement medicine"). No matter how we are paid, however, we are still physicians.

Name a profession with as much challenge and personal satisfaction. We are the helping profession, not the suing profession. Sure we get taken advantage of. The government, the third party payers, the lawyers, and the suit-happy public are driving us crazy, and even lowering our incomes, but some things can't be taken away from us.

We know the thrill of saving a life, a limb or an eye. We hear that precious first cry, and see the smiles of brand new parents. We share the peace of that great-grandmother dying with comfort and dignity. We can prevent heart attacks and cancer. We listen to the depressed soul sharing his most sensitive secrets. Our simplest reassurances and recommendations are powerful. We are trusted and needed, and we usually come through. It feels good.

We are indeed fortunate to be physicians. Let's not dwell on the negative and forget to be positive and constructive.

Medicine, America's greatest profession, is now challenged by this demand for "lowest bidder" services. Buckling under may cost us our pride and spirit. Colleagues, it's time to take a deep breath, smile, and prepare for battle with the fiscal "bottomliners," private and public.

If we don't rejuvenate and defend our ideals, we'll go on to become nothing but disgruntled wage-earners. We must maintain a professional attitude that incorporates our pride in traditional standards of quality medical care. We must stick together. And we must stick to our guns.

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Editor's Note Hear, hear!

MSMW

A Method of Reducing the Iodine Taste of Water Purified in the Wilderness

To the Editor: Kahn and Visscher[1] in this journal in 1975 presented a simple method of disinfecting water in the wilderness by the addition of small amounts of iodine. Subsequently Zemlyn, Wilson and Hellweg[2] reminded us that the iodine crystals are toxic and conceivably could be ingested. For this reason they urged the use of commercial tablets of tetraglycine hydroperiodide. A subsequent note by Beal[3] mentions the use of Povidone-iodine as a safe and inexpensive method of providing this material. Finally Jarroll, Bingham, and Meyer[4] showed that if the water is cold, the iodine may not completely destroy Giardia cysts and they feel boiling the water is safer.

Although boiling or some of the very elaborate filtration systems may be the preferable method, at times on the trail it is difficult to do this and the iodine treatment method provides a relatively satisfactory method to obtain disinfected water and is still recommended.[5] The major difficulty I have found with this method of purification is the rather nasty iodine taste that permeates any food or drink made from it. In a very short article in *Sports Afield,* (Kerasote T: "Camping: Modern Water Purification." *Sports Afield* 1980 Aug; 184:36) Ted Kerasote mentions that the addition of a pinch of sodium thiosulfate to a liter of treated water will neutralize the iodine and remove the taste, but this method requires the addition of another chemical, and probably is best to avoid.

Knowing that activated charcoal can remove many trace tastes and odors, I obtained some from an aquarium store and added approximately one teaspoonful of the material to a liter of water that had been previously treated with the usual iodine solution. I found that this material will absorb most if not all of the iodine taste and render the water much more palatable. Further there is no danger of toxicity. The charcoal is pro-

vided as rather large granules that are hard to drink. If it is drunk, charcoal is after all used as a universal antidote for poisons in many preparations and therefore certainly is not toxic to the body.

The material should be prepared as stated on the box—that is, put into water to wash away the fine charcoal dust that accumulates. The material is then dried. It weighs little and if kept in a lightweight plastic jar can be carried in a pack with no difficulty. Since backpackers have a great fetish for multiple uses, it is possible this material could be used also as an antidote for poison and even as a fire starter if necessary but since I have not tried either, I do not advocate them nor even feel that they are practical.

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Access to PaperChase

To the Editor: Since the article "Bringing the Medical Literature to Physicians—Self-Service Computerized Bibliographic Retrieval"[1] was published, physicians with personal computers and modems have written to us to ask how they could dial into PaperChase.

PaperChase is made available on a not-for-profit basis by the Beth Israel Hospital, Boston. Further information about PaperChase together with access numbers and a trial password can be obtained by calling the toll-free number (800) 722-2075, or by writing to the following address:

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Scuba Diver's Thigh or the Bends?

To the Editor: As a scuba diving instructor I was more than passingly interested in the letter from Dr Greenhouse and Ms Page in the November 1986 issue.[1] Their diagnosis of a special case of meralgia paresthetica, which they title "Scuba Diver's Thigh," sounds suspiciously like a classic case of the bends.

The bends are typically triggered by a too-rapid drop in ambient pressure. This allows nitrogen dissolved into the tissues to come out of solution faster than it can be transported to the lungs. If the released bubble were to manifest itself in the soft tissues surrounding the nerves it could create the pressure points Dr Greenhouse ascribes to the diver's weight belt. The amount of nitrogen dissolved into the various tissues is a function of the tissue type, pressure (due to depth of the dive) and the time spent breathing pressurized gasses.

With that in mind, I suspect the bends for two reasons.

First, and most important, the patient's dive was done to 80 feet for 50 minutes. As there was no mention of a decompression stop, I assume none was made.

If so, then the bends sounds quite likely. The US Navy decompression tables require a ten-minute stop at 10 feet specifically to allow a gradual release of microscopic nitrogen bubbles. The more conservative table used by the British Royal Navy goes off-scale and does not even list a decompression schedule for the dive she did. The closest listed dive (78 feet for 45 minutes) requires spending 5 minutes at 33 feet and an additional 25 minutes at 16 feet. Clearly, a dive to 80 feet for 50 minutes is not a wise thing to do.

It should also be pointed out that the above quoted decompression stops are for ocean diving only. If the dive was done at Lake Tahoe, which is near Dr Greenhouse's Reno practice, then additional factors are introduced. The two most significant of these are the decrease in atmospheric pressure due to the 6,000 foot altitude and the change in the specific gravity of the water. Under these conditions the US Navy required decompression schedule increases to one stop at 20 feet for 11 minutes followed by a second stop at 10 feet for 46 minutes. This is a total of 57 minutes in the water decompressing from a 50 minute dive. And again, the British table does not acknowledge the feasibility of the dive.

Presuming the dive was actually done in the ocean and the US Navy required decompression stops were completed, there still exists a possibility of the bends. The National Underwater Accident Data Council estimates the chances of the bends to be about 8 in 100,000, even when proper precautions are taken.

Second, the described symptoms of numbness lasting several weeks is classic to a bends hit caused by bubble formation in the vicinity of a nerve.

Contrast this to Dr Greenhouse's report of no similar cases of nerve damage due to weight belt pressure and the lack of abdominal enlargement, usually present with meralgia paresthetica.

As I am not a physician I won't go any further into the physiology. However, susceptibility to the bends is increased after its first occurrence. As such, I would like to suggest that Dr Greenhouse contact the Divers Alert Network (DAN) at Duke University Medical Center. They are a nonprofit organization dedicated to diving medicine and have both emergency phones (919) 684-8111 and an information line (919) 684-2948.

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REFERENCE

1. Greenhouse AH, Page K: Scuba diver's thigh (Correspondence). West J Med 1986 Nov; 145:698-699

* * *

Dr Greenhouse Responds

To the Editor: Mr Robert Fritz proposed that "Scuba Diver's Thigh"[1] was actually due to the bends. Regarding his comments, the dives were made at sea level by a person

very experienced in this sport who took all recommended precautions. The second dive was only to 25 or 30 feet. She has made numerous dives without difficulty both before and after the episodes in question and she developed the thigh numbness only when wearing the particular belt which I discussed and which was positioned exactly over the affected nerve.

Coincidence would be stressed beyond credibility to suggest that "a reasonable bubble in soft tissues surrounding the nerve" would occur in the same area only on the two occasions when this belt was worn and never before or since that time. Meralgia paresthetica invariably results from compression. A gas bubble miraculously finding its way to the same site twice is highly unlikely and I doubt that it could produce this syndrome under any circumstance.

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Body Odor Caused by Laundry Detergent

To the Editor: Body odor is a common, distressing and embarrassing phenomenon which is generally not talked about. A recent patient of mine, however, taught me something new about body odor.

Report of a Case

A 35-year-old man reported to me that for no apparent reason he had become aware of a very foul body odor problem some two weeks before coming to see me. Apparently his co-workers had also noted the problem and had mentioned it to him frequently. In spite of attempts to control this problem with a multitude of different antiperspirants and deodorants, the patient's problem persisted.

In an effort to discover the cause of this problem, routine laboratory tests were done; results were within normal limits. Getting back to basics, I found that the patient had started using Fresh Start laundry detergent. I suggested he try a different laundry detergent. He did so and immediately noted a resolution of his problem. He then related that, now that he was aware of the problem, he could put on some clothing washed in Fresh Start laundry detergent, and within moments some kind of chemical reaction occurring between his skin chemistry and the laundry detergent residue on the clothing would produce a very foul odor.

The patient is now using a different laundry detergent and the problem has resolved.

I report this case partly for those who might have a similar problem and may not have thought of this particular solution. I also report it because I believe that the thousands of chemicals to which we are subjected every day in cosmetic products, household chemicals and other industrial and business uses are frequently not tested for their many potentially serious or bothersome effects.

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Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

Definition of Hallucination

To the Editor: Drs Geoffrey L. Cummings and Bruce L. Miller's article on visual hallucinations[1] in the January issue was fascinating.

Under the category of differential diagnosis, the authors presented numerous causes for what they termed "hallucinatory visual changes" which ranged from ocular to central nervous system causes.

The definition of hallucination according to Dorland's Medical Dictionary is "a sense perception not founded upon objective reality." In the strictest sense many of these visual phenomena would be removed from the differential diagnosis if that definition were strictly adhered to from a medical standpoint as it most properly should be.

This does not detract at all from their fine article and the information it provides to the medical community; however, it is important to separate those disease processes that in fact have an actual pathologic basis from those that are perceived by the patient but have no objective founding in organic pathology.

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The Changing Dynamics of Graduate Medical Education

Implications for Decision-Making

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Cost-containment pressures and changes in traditional patient-care patterns are altering the process of graduate medical education. A thorough understanding of this process is a prerequisite to implementing changes that preserve the function of graduate medical education. This report describes the structure of the graduate medical education system and analyzes possible responses to the changes that are affecting it. The decision-making process within academic health centers is described, including an assessment of the roles of hospital directors, deans and faculty, as well as external regulatory agencies such as residency review committees, medical specialty boards and state licensing agencies. The activities of these participants are analyzed within the framework of the teaching hospital's service and education functions, and potential conflicts are described and illustrated by recent examples. Understanding the complex structure and functions of graduate medical education is a first step toward responding effectively to a changing environment.

(Gerbert B, Showstack JA, Chapman SA, et al: The changing dynamics of graduate medical education—Implications for decision-making. West J Med 1987 Mar; 146:368-373)

The system that delivers graduate medical education in the United States grew in a haphazard manner during the first part of the 20th century.[1] Mechanisms for funding graduate medical education, for accrediting residency programs, for licensing and certifying physicians' competence and for teaching residents in hospitals were all created independently. In spite of its random growth pattern, however, graduate medical education has functioned as a stable process.

This stability is now being threatened by effects of the health care fiscal "crisis." Before this crisis arose, graduate medical education was funded routinely from patient-care fees and government subsidies. Now, changes in third-party payment and reductions in state and federal funding have prompted closer examination of the ways in which graduate medical education dollars are spent. Questions are being raised about how many residents are necessary, how residents should function and which medical specialties are in demand—issues that have a direct financial impact on graduate medical education. Various proposals from the federal government (for example, from Congress, the executive branch and the Inspector General's Office), as well as activities in the private sector, suggest that there may soon be substantial changes in the way that graduate medical education is financed. As these changes take place, unresolved issues in the graduate medical education system are sure to come under sharp scrutiny.

In 1984 the Task Force on Academic Health Centers commissioned a report on the graduate medical education system.[2] In compiling this report, we were asked to provide an in-depth examination of the decision-making process and participants in graduate medical education today. To do so, we reviewed relevant literature and interviewed persons across the country who play key roles in the graduate medical education system.* Our draft report was distributed widely in an effort to validate our findings, and we continued to revise the written document until consensus was achieved regarding the accuracy of our description.

As data were collected, it was found that often key persons within one part of the system did not understand how graduate medical education works on a larger scale, that many held erroneous beliefs about the process of graduate medical education and that policymakers were making decisions while unaware of some crucial interdependencies in the system. Nevertheless, it was clear throughout the course of our research that the people with responsibility for graduate medical education are eager to bridge the gap between what they now know and what they must learn to continue to have a robust system.

By elucidating the structure of graduate medical education and the problems inherent in the graduate medical education process, this paper is intended as a tool for those who will guide the system through the period of transition that has already begun. To provide a starting point, we first describe how the financial crisis in health care has affected the graduate medical education system.

*Numerous persons at academic health centers, government agencies and regulatory bodies within the medical education system contributed to this report by giving generously of their time and professional knowledge.

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This work was undertaken for the Task Force on Academic Health Centers, The Commonwealth Fund. The views expressed are those of the authors and do not necessarily represent the views of the Task Force or of its individual members.

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Effects of Changes in Medical Care Payment

New ways of funding health care have already altered the pattern of graduate medical education. One immediate effect has been to make its costs more visible. The previous indirect subsidy of graduate medical education by patient-care dollars (and in some institutions by research funds) is no longer assured. Instead, as hospital payment has shifted to fixed price per admission (Medicare) or selective contracting, the costs of graduate medical education have become more clearly separated from other expenses. A prime target for reduction in the federal budget is funding of health manpower training. Additional pressure has been brought to bear by reductions in state revenues. These changes are reflected in budget cuts to state-supported medical schools, which in turn may reduce support of residency programs. In California, for example, the state legislature has reduced all state-supported funding for non-primary care graduate medical education programs for each of the past three years.

The University Hospital as Competitor for Health Care Dollars

Changes in the funding of patient care have also encouraged the growth of health maintenance organizations, for-profit hospital chains, and price-competitive contracts for patients in hospital. As a result, there has been increasing pressure for academic health centers to compete for a portion of the health care market. They are at a disadvantage in this arena, however, because their costs of care appear to be greater than in nonteaching hospitals. In effect, patients may be directed away from teaching hospitals, as exemplified by a recent corporate publication for employees (The Quaker Oats Company: Informed Choices, Chicago, 1985) on how to lower health care costs. The publication includes the following admonition: "If it's a teaching hospital, you can count on its prices being two or three times as high as a non-teaching hospital. Teaching hospitals are not necessary for routine care or surgery." Another example is the Select Care plans of Blue Cross/Blue Shield of Maryland, which accept only low cost hospitals, thereby excluding the Johns Hopkins Hospital (Burns MK: "Blue Cross Unveils Plan to Cut Costs," *Baltimore Sun*, May 1, 1984, pA1).

Altered Patterns of Patient Care

New financial incentives have led to altered patterns of patient care, a process that in teaching hospitals has had important consequences for graduate medical education.[3] Hospital length of stay is declining as payment-per-admission creates incentives to transfer patients who require convalescent care to extended care facilities, nursing homes or their own homes.

To assure the flow of patients, academic health centers must continue to develop and market specialized services that are not yet available in the community, such as bone marrow transplantation and sophisticated radiologic diagnostic facilities. This emphasis on specialized care may result in training experiences for residents that lean toward greater exposure to critically ill patients and those with unusual problems, and away from patients with problems that are more likely to be seen in subsequent practice.

Aside from these changes in patient care, the very real prospect of "losing business" has prompted hospital directors and their boards to reconsider the service and educational functions of their institutions. Chief executive officers are starting to assess the benefits and drawbacks of employing residents and are beginning to consider the potential conflict between training residents and providing cost-effective care. These issues are not easily resolved, and the data needed to resolve them are not readily available.

Scope and Purpose of Graduate Medical Education

Although graduate medical education was first established around the turn of the century, it was not until after World War II that the number of residency programs and positions began to rise rapidly in response to the growing demand for advanced training beyond the internship. From 1950-1951 to 1973-1974, the number of residency positions grew from 29,000 to 66,000. By 1983 the approximately 4,800 approved residency programs in the United States offered nearly 75,000 residency positions.

This rapid rise in the number of residents was spurred largely by the need of teaching hospitals to provide patient care services at the lowest possible expense. The perception of residents as a labor resource has placed them in the dual roles of employee and student. Since residents' labor is essentially purchased by the hospital, it could be argued that the service function of housestaff overrides their education goals. The intellectual and philosophical considerations crucial to a physician's training, however, clearly fall within the educational scope and outside of a hospital's responsibility to its staff.

Even the courts have had difficulty in deciding whether the resident is considered an employee or a student. In a recent court case concerning the tax status of stipends, the California State Court of Appeal ruled that housestaff are primarily students, overturning a decision by the Public Employment Relations Board that housestaff are employees.[4] The appeal ruling held that residents' service function is subordinate to their education experiences.

The Decision-Making Process in Graduate Medical Education

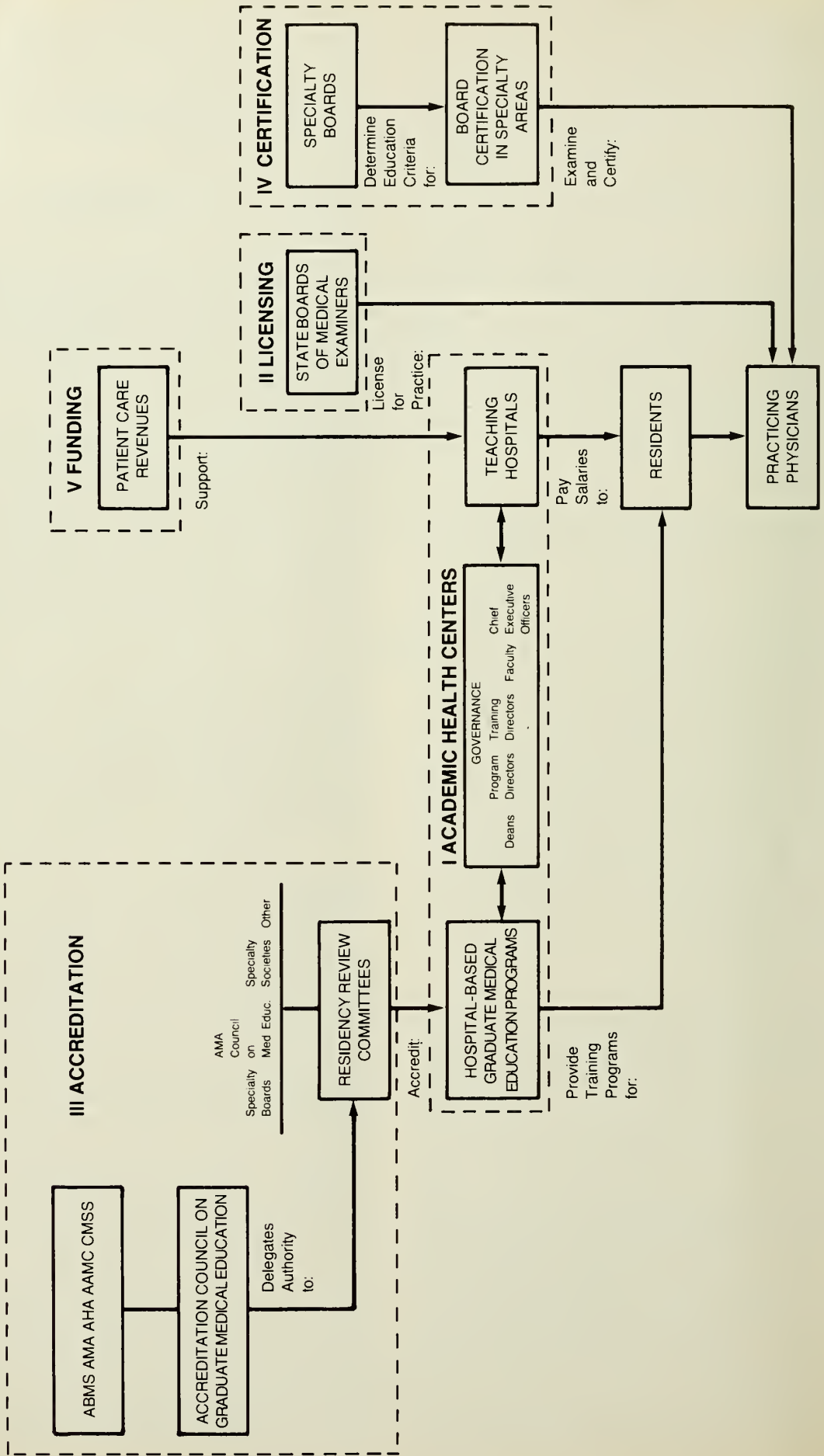
The numerous groups and individual persons who act as decision makers in graduate medical education, and their relationships to one another, are depicted in Figure 1. This figure shows the key decision makers within the academic health centers (area I), those who license physicians to practice (area II), those who accredit residency programs (area III), those who examine and certify residency graduates for practice in medical specialties (area IV) and, finally, those who pay for graduate medical education (area V).

Key Decision Makers Within the Academic Health Center

Decision makers within academic health centers (Figure 1, area I) have a major influence on the number of positions available within residency programs and the content of those programs. Depending upon the structure of the institution and on other factors described below, the size and content of residency programs are governed to varying degrees by the dean of the medical school, the chief executive officer of the teaching hospital, program directors for each residency program and training directors who work under the program directors to administer housestaff education within a department. These persons' comparative influence on graduate medical education varies among institutions.

Figure 1

PARTICIPANTS IN THE GRADUATE MEDICAL EDUCATION SYSTEM*



*Adapted from **PRESCRIPTION FOR CHANGE: Report of the Task Force on Academic Health Centers.** The Commonwealth Fund, 1985.

Determining the Number of Residents. The chief executive officer, whose first concern is the service needs of the hospital, can be a key figure in determining the number of positions available in residency programs. This is most true in institutions that use a formula to establish program size. Although not common, these formulas, which are based on the number of beds per service or some variation thereof and are calculated annually, place the control of the number of residents, both total and per service, primarily under the jurisdiction of hospital management.

Some institutions have frozen the total number of residents funded through hospital revenue. Departments that wish to have more residents than the number allocated must fund the additional positions through mechanisms other than patient care revenue from the hospital.

In the absence of a formula, certain decision makers exercise greater influence than others. For example, in those hospitals where faculty practice plans or other medical-school dollars contribute to housestaff training, the dean may play a major role in determining the number of residents. The dean may be influenced in this calculation by the number of residents needed to maintain an adequate teaching staff for medical students.

Although program directors usually have limited control over the size of their programs, each department's stature with hospital chief executive officers and deans may be influenced by the generation of research or practice plan funds as well as by historical allegiances. The decision-making role of faculty also rests to a large degree on the extent to which practice-plan income contributes to funding. Like the dean and program director, faculty want sufficient staff to fulfill the department's teaching requirements, but they also want to ensure sufficient time to pursue research. It has also been suggested that some faculty's desire to "replicate" themselves through residents may motivate them to lobby for more residents than are actually needed to meet the service needs of the hospital or the manpower needs of their specialty.[5]

Establishing the Content of Residency Programs. To meet service needs, chief executive officers hire residents to staff certain units or services, such as intensive care units or emergency rooms. Such channeling of resident manpower may not necessarily coincide with an optimal educational program.

Once the service needs of the hospital have been determined, program directors are the most active decision-makers in deciding what residents will learn. Most program directors serve as both the medical school department chair and chief of that service in the teaching hospital; as such, they often have day-to-day input into the content of residents' experiences.

Key Participants Outside the Academic Health Center

The academic health center is not autonomous in its decision making. External agencies that license physicians, accredit residency programs and issue specialty certificates influence both the size and content of graduate medical education programs. These regulatory agencies are located either within state government (licensing authorities) or in the private sector (accrediting and certifying authorities).

As shown in Figure 1, the licensure (area II), accreditation (area III) and certification systems (area IV) function as separate gatekeepers in the graduate medical education system. In general their responsibilities are distinct; overlaps among the systems are minimal and informal.

Licensure. As a prerequisite to licensure (area II), most states require one or more years of accredited residency training as well as a passing score on all three examinations of the National Board of Medical Examiners. No other test is necessary, although graduates who have not taken National Boards must pass the Federation Licensing Examination.

Accreditation of Residency Programs. The Accreditation Council for Graduate Medical Education (ACGME) is responsible for accrediting and reviewing programs in graduate medical education. The ACGME is composed of representatives of five organizations: (1) the American Medical Association, (2) the American Hospital Association, (3) the Council of Medical Specialty Societies, (4) the American Board of Medical Specialties and (5) the Association of American Medical Colleges. The ACGME has the authority to delegate its responsibility to residency review committees within each of 23 specialty fields. All of the residency review committees have requested and been granted this authority. The residency review committees are composed of members appointed by (1) the Council on Medical Education of the American Medical Association, (2) the appropriate specialty board and, in some cases, (3) the specialty society (for example, the American College of Surgeons). (See Figure 1, area III.)

Each residency program must conform to a set of general and specialty-specific requirements, which together are labeled "The Essentials of Residencies," published by the ACGME and often called "The Green Book."[6] The general requirements, created by the ACGME, must be complied with by all graduate medical education programs. The special requirements, prepared by the residency review committees, generally concern faculty, administration and program content; occasionally they also stipulate required numbers of procedures per resident. Each residency review committee also stipulates a minimum length of program, ranging from three years for some specialties (such as internal medicine) to six years (for example, neurosurgery).

Special requirements are changed as deemed necessary by the residency review committees, but must also be approved by the ACGME. All changes are reviewed by the parent organizations (the specialty board and in some instances the specialty society) for comments, but these organizations, unlike the ACGME, cannot mandate changes or veto residency review committee decisions. Examples of recent changes in requirements include increases in the training period for anesthesiology, urology, neurosurgery and radiology.

After periodic review, a residency review committee may withdraw a program's accreditation or place it on probation for failure to meet general or special requirements. Such actions may be appealed through a process established by the ACGME.

Certification of Specialists. The medical specialty boards (Figure 1, area IV) also influence the residency training process. Certification by medical specialty boards designates a physician as having met requirements specified by the board and having successfully completed an accredited residency program. There are currently 23 specialty boards offering 31 types of general and 42 types of subspecialty certifications. To date, seven boards issue time-limited specialty certificates; 12 boards have approved plans for recertification procedures. No board has a procedure, however, that would remove previous certification from a physician.

Although physicians need not be board certified to practice a specialty, programs have some investment in their grad-

uates passing the board examinations; some residency review committees (for instance, general surgery) do include review of specialty board certification rates as an evaluation criterion for accrediting programs. Most residency review committees' special requirements state that certification rates are important.

There are other strong incentives for board certification. In some hospitals the certification system is linked to obtaining hospital privileges.[7] Malpractice premiums are sometimes keyed to specialty certification, with premiums varying according to the risks involved. Board certification may enhance employment possibilities if health maintenance organizations and medical care corporations increasingly come to use board certification as a hiring criterion. The public is also becoming more aware of the distinction of board certification.

There is no official relationship between medical specialty boards and residency review committees, but the two groups do work together for the most part when changes are made. For example, when the American Board of Radiology recently increased its residency training requirement from three to four years, the residency review committee subsequently made a similar change.

The Federal Trade Commission and Antitrust Laws. One mission of the Federal Trade Commission is to ensure that nongovernmental entities do not restrain persons from earning a livelihood in a given career. In medicine, the Federal Trade Commission monitors the policies of the accrediting and certifying bodies for potential exclusionary biases. They are especially vigilant for policies that may limit the number of persons entering a residency in a specialty of their choice. Thus, residency review committee requirements must be based on improving the quality of the educational experience and cannot directly restrict numbers within a specialty. The Federal Trade Commission also ensures that physicians can practice any specialty they choose, whether or not such physicians are board certified. In the past eight years the Federal Trade Commission has not seen a need to take action for restraint of trade against the program accreditation or physician certification systems. Nevertheless, the fear of being in violation of restraint-of-trade statutes is a powerful deterrent to attempts to adjust the numbers of residents according to specialty.

Problems Inherent in the Graduate Medical Education Decision-Making Process

A simple scanning of Figure 1 shows that there are no formal connections or lines of communication among key participants in the graduate medical education system. The absence of linkage between the component that funds residents and other areas in the system is particularly noteworthy. This means that residency review committees and boards can make decisions that affect the cost of training residents without first assessing the financial impact of such decisions and without collaborating with those who must implement the changes. Furthermore, problems among participants are difficult to resolve since there is no overriding authority to settle differences.

At teaching hospitals, the basic conflict demonstrated by Figure 1 is the difficulty of balancing service needs of hospitals with the educational needs (as set out by residency review committees and boards) of residents. Those who pay for graduate medical education and their "representative" at the hospital, the chief executive officer, are concerned with providing high quality patient care at the lowest possible cost. Others in the system are responsible for identifying what residents need to know and how they can learn it. This conflict of interest leads us back to the question of whether residents are employees, and therefore under the supervision of the hospital and its chief executive officer, or students, whose activities should be guided by the medical school as well as by the residency review committees and boards. It is obvious that the issue is not clear-cut and will not be fully resolved by a legal determination that residents are only employees or only students.

In the recent past, a variety of participants in the graduate medical education system have had minor policy disagreements with residency review committees or boards. Two disputes are described to convey a sense of the types of issues that arise when decision-makers have conflicting objectives. The examples given represent relatively minor problems but indicate the potential for more serious dilemmas as the education and service functions of hospitals become more discrepant.

The first example illustrates a discrepancy in goals between program and hospital management and members of the pediatrics residency review committee. During the 1970s, hospital chief executive officers assigned pediatric residents to staff neonatal and pediatric intensive care units in order to meet patient care needs. A number of program directors believed that many residents were spending a disproportionate amount of training time in intensive care units, to the detriment of the overall educational endeavor. In 1978 a Task Force on Pediatric Training determined that more than six months of intensive-care-unit experience was excessive.[8] Thus, the Pediatric Residency Review Committee now requires that the maximum amount of time a resident may spend in the intensive care unit is six months. The means of providing any required extra coverage was left to the hospital's discretion.

A second example involves a lack of parallelism in board and residency review committee requirements. Such a conflict is unusual, since actions by one group are typically followed by similar changes by the other and since many members sit on both bodies. The problem began when the American Board of Pathology increased the number of years required for board certification from four to five. The Board believed that the change was necessary to keep residents abreast of the information explosion in pathology and to preserve the status of pathology within the academic community. Members of the residency review committee and many academic pathologists felt, however, that they had not been adequately consulted before this change and that the board had been too hasty in this move. It was asserted that an impact report had not been fully developed and that the consequences of this change, including its financial impact, had not been explored. Colloton[9] predicted that this one change in requirements could cost teaching hospitals $21.3 million.

Conclusion

The conflict between meeting educational goals and satisfying the service-delivery mission of the hospital is perhaps the most pressing dilemma facing graduate medical education today. Teaching hospitals, determined to maintain their competitive edge, may elect to increase their technologic, intensive care and subspecialty capabilities. Two major unintended consequences appear to be emerging from these trends. First,

the disproportionate emphasis on specialty training in hospitals may leave the need for primary care physicians unmet.[10] Hospitals will continue to reap greater financial benefits from training specialists who carry out more procedures and provide services that are reimbursed at a higher level. Second, the training that many residents receive may become increasingly discrepant from that needed to ensure their success in future practice.[3]

Resolution of the issues raised in this article will require the cooperative effort of individual persons and groups who have distinctly different goals and interests. Yet the prospect of productive interaction is dim as long as the graduate medical education system continues to function without systematic communication or leadership. To effect positive changes while preserving the vitality of graduate medical education, a process that encourages a planned and coordinated transition needs to be found.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Epikeratophakia in Children

QUESTION:

Is epikeratophakia, a form of refractive surgery that alters the anterior surface of the cornea with a preground donor tissue lens, accepted medical practice for the treatment of aphakia in children?

OPINION:

In the opinion of the Scientific Advisory Panel on Ophthalmology, epikeratophakia, a new form of refractive surgery, is gaining increasing acceptance as one alternative for the optical correction of aphakia in children following cataract removal. In epikeratophakia, the anterior surface of the cornea is altered by adding a machine-lathed donor tissue lens. Because it is a form of lamellar keratoplasty, the refractive error can be changed without carrying out intraocular surgery.

Research and experience to date indicate that this promising procedure may offer an exciting and potentially useful alternative to the difficult problem of fitting very young children with contact lenses. However, the results are still not well defined. Further refinements are necessary before full accuracy and stability can be obtained. It is difficult to analyze the result of this technique because it continues to evolve and there is lack of long-term follow-up. Obviously, further longitudinal studies are necessary.

Furthermore, in very young children, it is difficult or impossible to assess how well such a technique actually restores vision; technical success is easier to ascertain than visual success. Until the visual success rates can be determined to be as good as the technical success rates would indicate, epikeratophakia in children should be considered an investigational procedure that may have value for certain selected situations.

Special Article

The Epidemiology of Firearm Deaths Among Residents of California

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Firearms are a leading cause of death in the United States, yet the effort to understand their aggregate impact on the public's health has only just begun. There were 26,442 firearm deaths among California residents during the years 1977 through 1983. During this period firearms were the eighth leading cause of death for California as a whole, sixth for male Californians and first for black males aged 15 to 34 years and black females aged 15 to 24 years. A plurality of firearm deaths were suicides; unintentional deaths contributed only 3% of the total. Black men aged 25 to 34 years had the single highest firearm mortality rate; 80% of firearm deaths in that group were homicides. Men 75 years old and older had the highest firearm mortality rate when all races were considered together, however, and 93% of firearm deaths in that group were suicides. The discussion focuses on our current understanding of firearms as a medical and public health problem and suggests directions for future research and intervention.

(Wintemute GJ, Teret SP, Kraus JF: The epidemiology of firearm deaths among residents of California [Special Article]. West J Med 1987 Mar; 146:374-377)

Firearms are a leading cause of death and disability in the United States. Each year more than 30,000 Americans die as a result of gunfire. More than 100,000 injuries have been estimated to occur annually from unintentional shootings alone.[1] With few exceptions[2-4] epidemiologic analyses of firearm mortality have considered only one aspect of the problem, separating murders from suicides from unintentional deaths.

This article analyzes the 26,442 firearm deaths that occurred to California residents from 1977 through 1983. It focuses on the vehicle common to these deaths—the gun—in an effort to provide a clearer estimate of the impact of firearms on the public's health. By de-emphasizing the behavioral aspects of firearm deaths, this unifying approach also promotes the consideration of prevention strategies beyond those addressing the behavior of persons actually involved in shootings. It may well be that here, as elsewhere in medicine and public health, the most effective preventive measures do not attempt to modify the behavior of those to be protected.

Methods

Data from death certificates for all deaths occurring to California residents from 1977 through 1983 were obtained by a computerized search of the California Master Mortality File. The 1980 census data for California were used for a mid-interval population; intercensal estimates were obtained from the Population Research Unit, California State Department of Finance.

The study period spanned the transition from the 8th to 9th edition of *The International Classification of Diseases*, but no coding changes affected firearm death ascertainment. The following types of firearm deaths, listed with their *ICD* "E" (external cause) codes, were included in the study: unintentional deaths (E922), suicides (E955.0 to E955.4), homicides (E965.0 to E965.4) and deaths of undetermined intent (E985.0 to E985.4). Firearm deaths by legal intervention (E970) and those resulting from operations of war (E991) were excluded. (The *ICD* rubric for unintentional firearm deaths includes the rare peacetime deaths that occur among military personnel during training.) Delayed firearm deaths were perforce excluded as they are not coded separately from other delayed deaths from external causes. The combined exclusions accounted for less than 5% of firearm deaths.

The leading causes of death for Californians* were reranked, listing firearms separately and excluding firearm deaths from those categories in which they would otherwise be found. Nonfirearm suicides and homicides were combined into a "nonfirearm intentional death" category. Standardized mortality ratios were used as a summary measure of the evenness of distribution of firearm deaths across race and gender groups. Years of potential life lost were calculated using the method employed by the Centers for Disease Control.[5]

Three limitations resulting from this study's reliance on death certificate data should be noted. While diagnostic accuracy for firearm deaths should be high, as virtually all these death certificates were signed by a coroner following an investigation and autopsy, accuracy for nonfirearm causes of death

*The definitions employed were those of the California State Center for Health Statistics, which are virtually identical to those used by the National Center for Health Statistics.

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may be lower.[6] Second, this article does not report separate results for Hispanics. California vital statistics do not categorize Hispanics separately, but classify them as white unless a different racial origin is noted on the death certificate. Finally, separate results for handguns, rifles, shotguns and other firearms are not presented, as the type of firearm involved was reported in only 20% of firearm deaths.

Results

Firearms caused 26,442 deaths among California residents during the years 1977 to 1983—2% of all deaths in that population. The mean annual crude firearm mortality rate was 16.0 per 100,000 population. Rates for individual years ranged from 14.4 per 100,000 population in 1983 to 17.2 per 100,000 population in 1980; no consistent trend was observed.

Males accounted for 84% of firearm deaths, and had a mortality rate of 27.1 per 100,000 population; the rate for all females was 5.1 per 100,000 population. Age- and gender-specific rates are presented in Table 1. A bimodal pattern in risk existed for males. Men 75 years old and older had the highest firearm mortality rate, followed by young adult men aged 25 to 34 years. For women, a single peak in the 25- to 34-year age group occurred. Rates for both boys and girls younger than 15 were substantially lower than those for all other age groups.

Race- and gender-specific results are presented in Table 2. The mortality rate for blacks was as much as ten times that for some other racial groups. Blacks suffered nearly 2.5 times as many firearm deaths (an excess of 415 deaths each year) as would have been seen if their age-specific firearm mortality rates had equaled those for all Californians combined.

Age- and race-specific rates for males are shown in Figure 1. Black men aged 25 to 34 had a mortality rate of 135 per 100,000 population, more than three times that for the group at next highest risk and more than eight times that for the state as a whole. Rates were highest for blacks in all age groups except those over 75; the finding that the rate for all male Californians combined was highest over age 75 (Table 1) derived from the increased mortality in that age group among whites. Mortality rates for other races tended to be maximal in young adulthood and decline or remain relatively stable thereafter. (Firearm mortality rates for Asian, Native American and "other" boys aged 5 to 14 and for "other" boys under age 5 were all less than 1.0 per 100,000 population. No firearm deaths occurred among Asian or Native American boys under age 5, or among Native American men aged 75 and older.)

Among female Californians, firearm mortality rates were greatest for blacks in all age groups. Black women aged 25 to 34 had the highest female rate observed, 17.4 per 100,000 population. Rates for females of all races were highest for ages 15 to 34 and declined thereafter.

Firearms and the Causes of Violent Death

Firearms were the leading cause of intentional death in the state, accounting for 54% of all suicides and homicides combined. Firearms were used in 59% of all California homicides. Among persons aged 15 to 34, the high-risk group for homicide in California, 65% of these deaths were attributable

TABLE 1.—*Firearm Mortality Rates* by Age and Gender, and Male:Female Rate Ratios by Age for Californians, 1977-1983*

Age in Years	Both	Gender: Male	Gender: Female	M:F Rate Ratio
<1	0.34	0.37	0.31	1.2
1-4	0.55	0.67	0.42	1.6
5-14	1.69	2.59	0.75	3.5
15-24	22.73	37.73	6.89	5.5
25-34	24.23	40.85	7.29	5.6
35-44	19.26	31.38	7.18	4.4
45-54	16.69	27.02	6.75	4.0
55-64	14.62	24.83	5.41	4.6
65-74	16.00	30.90	4.25	7.3
75 +	17.04	44.65	1.79	24.9

*Rates are per 100,000 population per year.

TABLE 2.—*Firearm Deaths Observed, Firearm Mortality Rates, Male: Female Rate Ratios and Standardized Mortality Ratios, by Race and Gender for Californians, 1977-1983*

	Deaths Observed	Mortality Rate	M:F Rate Ratio	Standardized Mortality Ratio
Total	26,442	16.0	5.3	—
Male	22,155	27.1		—
Female	4,287	5.1		—
White	20,896	16.6	5.2	1.02
Male	17,402	28.1		1.02
Female	3,494	5.4		1.06
Black	4,875	38.3	6.6	2.48
Male	4,206	67.5		2.61
Female	669	10.3		2.05
Asian	297	3.6	4.5	0.22
Male	242	5.9		0.22
Female	55	1.3		0.24
Native American	100	7.1	5.0	0.45
Male	83	12.0		0.46
Female	17	2.4		0.47
Other	274	1.6	4.2	0.11
Male	222	2.5		0.10
Female	52	0.6		0.13

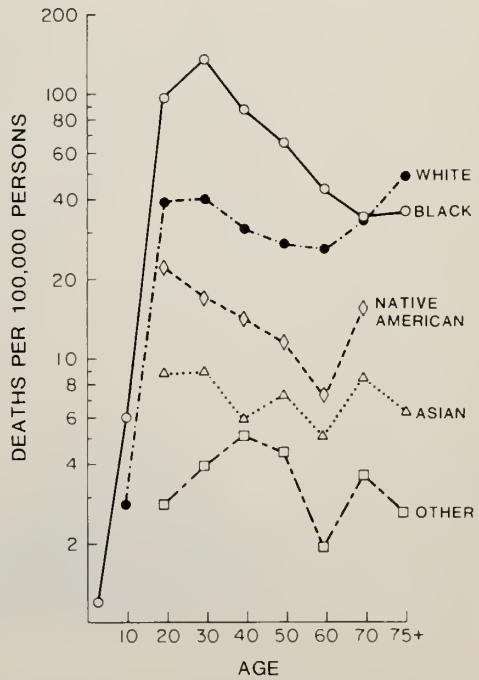

Figure 1.—Firearm mortality rates for male Californians by race and age, 1977-1983

to firearms. Of all suicides, 49% were firearm-related; this percentage remained relatively stable across all age groups.

A plurality of firearm deaths were suicides. Suicides accounted for 12,798 deaths over the study period, or 48% of all firearm deaths. Homicide ranked second with 12,329 deaths, 47% of the total. Unintentional shootings accounted for only 688 deaths, 3% of all firearm deaths. There were 2% classified as undetermined.

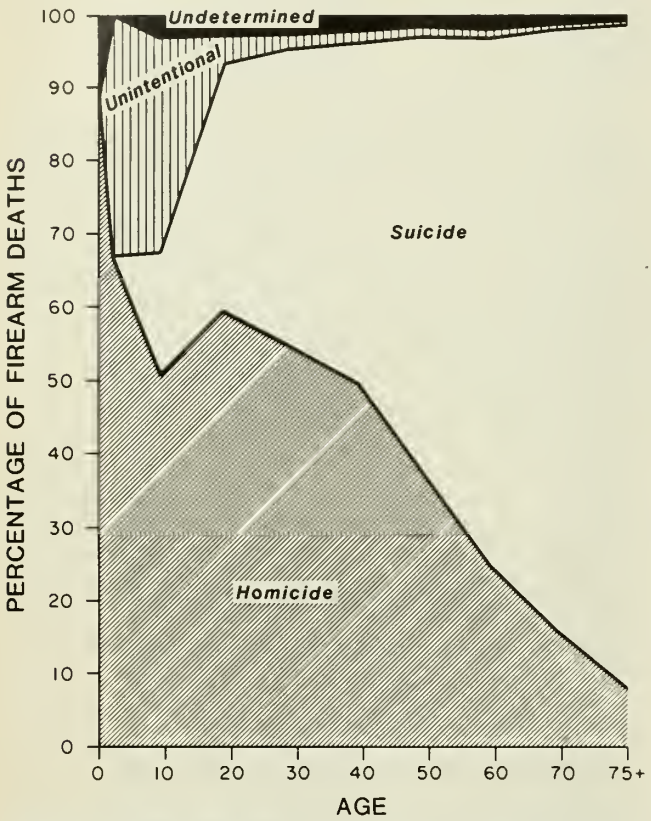

Figure 2.—Percentage distribution of firearm deaths by cause and age for Californians, 1977-1983

The percentage of all firearm deaths attributable to homicide, suicide or unintentional shootings was related to age, as shown in Figure 2. Under age 1, a total of 89% of all firearm deaths were homicides. The percentage contribution of firearm homicide to overall firearm mortality dropped steadily thereafter except during young adulthood. Among persons aged 75 and older, 90% of firearm deaths were suicides. Unintentional firearm deaths were most prominent among children and young adults; 61% of these deaths occurred to persons aged 1 to 24 years.

The distribution of firearm deaths by cause was related to race as well. Among whites, firearm suicides outnumbered homicides by almost 50%; there were 11,863 firearm suicides and 8,041 firearm homicides in this group. For every other racial group, homicides were more frequent. Among blacks there were 3,884 firearm homicides and 702 firearm suicides, a more than fivefold difference.

As a result of these effects, the relative contribution of firearm homicide, suicide and unintentional death varied among the groups at highest risk for a firearm death. For black men aged 25 to 34, a total of 80% of firearm deaths were homicides; only 12% were suicides. Yet for white men that same age, suicides outnumbered homicides and accounted for 48% of all firearm deaths. Among men 75 years old and above, 93% of all firearm deaths were suicides.

Firearms Among Other Causes of Death

Firearms ranked as the eighth leading cause of death for California residents as a whole, sixth for males, second for all persons aged 15 to 34 and first for black males aged 15 to 34 and black females aged 15 to 24. Figure 3 displays the distribution of the major causes of death for persons aged 5 to 54. Firearms accounted for 43% of all deaths among young black men aged 15 to 24 and 19% of deaths in that age group for the state as a whole.

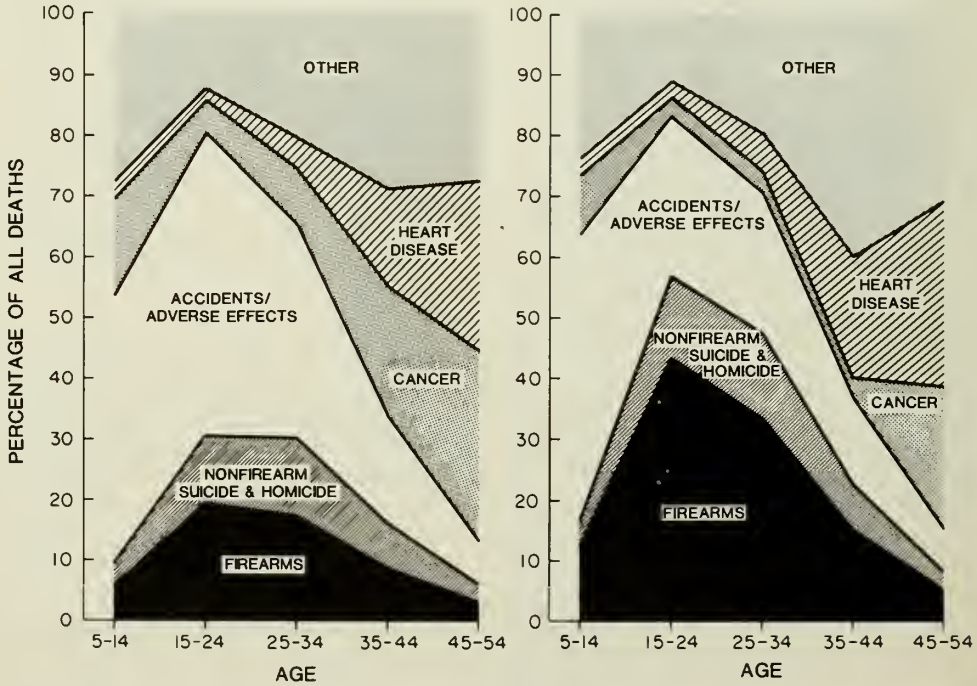

Figure 3.—Percentage of all deaths attributable to each of several leading causes of death. **Left**, Californians, 1977-1983. **Right**, black male Californians, 1977-1983

Firearm deaths among black males resulted in 139,866 years of potential life lost over the study period. By this measure, firearms were the leading cause of premature death for black men and boys. Firearms ranked fourth among causes of premature death for all California residents combined, accounting for 746,705 years of potential life lost. If the firearm mortality rates observed in this study were to remain unchanged indefinitely, 1 in 22 black and 1 in 43 white males born between 1977 and 1983 would suffer a firearm-related death by age 75.

Discussion

The central hypothesis of this study was that examining firearm deaths in aggregate would lead to a clearer picture of the effect of firearms on the public's health. Firearms emerge as a major public health problem. They are the number one cause of death for some segments of the population of California and are among the top ten causes of death for the state as a whole. California is not atypical in this regard; its rates for firearm homicide, suicide and unintentional death are all close to the median for the 50 states.[7]

It was further hypothesized that this approach might yield useful insights into our current efforts to prevent firearm deaths and injuries and suggest directions for the future. This has also occurred.

Suicide was the leading mode of firearm death in this study. It may therefore be inappropriate to rely primarily on criminal justice approaches to firearm deaths and injuries. In fact, such approaches may be inherently limited in their effectiveness against criminal shootings as well. The Federal Bureau of Investigation has underscored this point, stating that "it has long been recognized that murder is primarily a societal problem over which law enforcement has little or no control."[8]

Only 3% of the firearm deaths in this study were unintentional. In 1982 unintentional shootings accounted for only 6% of firearm deaths nationally (National Center for Health Statistics, unpublished data, June 1984). Therefore, it is unlikely that expanded educational efforts to promote the safe use of firearms will lead to significant future reductions in firearm deaths.

There are multiple high-risk groups for a firearm death. These groups differ from one another not only in age, race and gender, but in the types of firearm death for which they are particularly at risk. Prevention strategies targeted specifically at high-risk groups will need to include all these factors.

Such findings support preventive measures directed against firearms themselves. All firearm deaths, however they may otherwise be classified, are by definition associated with a common vehicle of transmission. By analogy, control of many infectious diseases has been dependent upon control of an associated vector. Motor vehicle-related deaths and injuries were substantially reduced by improvements in the design of motor vehicles, rather than efforts to change the behavior of persons using them.[9]

Restricting the availability of firearms, and particularly handguns, is one such measure. In a major study prepared for Congress, the General Accounting Office cited handgun availability as a major determinant of rising firearm homicide rates.[10] A subsequent special study of firearm suicide[11] has yielded supportive results.

Attention to the design of firearms themselves may be beneficial. The Maryland Court of Appeals found in 1985 that a Saturday night special—the highly concealable handgun that was a special target of the Gun Control Act of 1968—constitutes an unreasonably dangerous product. Its manufacturer and distributors may therefore be held liable for harm resulting from its use.[12]

Physicians and other health professionals are uniquely able to bring information on the health effects of firearms to their patients and the public. The dangers inherent in having firearms in the home can be made clear to patients as a part of basic health education. When a major family conflict arises or a patient is seriously depressed, a special effort can be made to ascertain whether there are firearms in the home and to have them removed.

Health professionals can have their greatest effect by initiating communitywide efforts and legislative action. Widespread public support for greater control of firearms has been documented repeatedly.[13,14] The lack of a stable, visible constituency for change has often prevented this support from being translated into public policy.

By emphasizing that firearms are a major public health problem, concerned health professionals can reverse this trend. Through research such as that presented here, they can bring to light the full impact of firearms on health and guide the evolution of public policy in this area. They can promote widespread public awareness at the local level through coalitions with other community leaders. They can educate their local, state and national legislators. They can encourage their state medical societies and similar organizations to become active advocates for measures to minimize the health problem created by firearms. And they can create a new professional association to promote and coordinate all these efforts.

Few health issues in our recent history have engendered as complex and lasting a controversy as that surrounding the prevention of firearm deaths and injuries. Through individual and collective action, health professionals can become a potent force to control this epidemic of modern times.

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Pioneer Transfusionists of Los Angeles

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The transfusion of blood from one person to another is an accomplishment that had been dreamed of by many physicians for centuries but has only relatively recently been achieved. The first transfusion (animal to human) was given by Jean Denys of Paris in 1666[1] and was followed by a number of transfusions, some in France, but most in England. The danger of the procedure, however, was such that only about 300 transfusions had been given by the end of the 19th century, and many of those were fatal. The mortality was caused partly by the lack of knowledge of blood groups and partly because blood transfusion was limited to those cases in extremis.[2]

Although a few early attempts had been made as a measure of desperation, blood transfusion in the United States really began with the arteriovenous anastomosis performed by Alexis Carrel in 1908.[3] This was followed by the pioneering efforts of G.W. Crile, who wrote the first book published in America on this subject.[4] Crile, as did a number of his colleagues, used an arteriovenous anastomosis to transfer the blood from donor to recipient. Due to the difficulty of this surgical procedure and the trauma to the donor's artery, which was lost for further use, it was used infrequently and by only a few workers. Subsequently, the multiple-syringe method of Lindeman[5] (a modification of Seeman's earlier method)[6] allowed blood to be taken repeatedly from a donor's vein without the radial artery being permanently damaged, and was thus better accepted. The technical aspects of the procedure were less demanding and achievable by less specialized workers.

Early in this century there were only a few physicians in this country who did blood transfusions, and they managed to create a subspecialty out of the field. Some of these persons were Crile of Cleveland, Unger of New York, Minot of Boston, Curtis of Chicago and Ochsner of New Orleans. There was of course a need for such work in every major city, and in Los Angeles, the opportunity devolved on the pioneering pathologists Walter Brem and A. Hermann Zeiler.[7]

These two physicians were about as diverse as two men could be. Brem was the prototypic polished Southern gentleman. Born in North Carolina in 1875, he received a baccalaureate degree in science from the University of North Carolina in 1896. After serving in the Spanish-American War, he attended medical school at Johns Hopkins University (Baltimore), after which he became a house officer at the University Hospital under William Osler.

Zeiler was born in 1882 in the town of Sombor, Yugoslavia. At the age of 5, his parents brought him to Leadville, Colorado. On graduating from high school, the youthful student went directly to the College of Physicians and Surgeons in New York City, where he obtained his medical degree in 1905. He interned at Sydenham Hospital in New York City for about six months.

After their training, both physicians decided to take their first job in the Canal Zone. The reasons for this undoubtedly are as complex as the reasons for any decision made by humans. On the other hand, it is possible to surmise some of the reasons. For Brem we can see a rather continuous series of stimuli. During this time the rise in technology in medicine was such that the clinical laboratory was becoming of great interest.[8] Reisner[9] shows that the advent of the microscope in the mid-1800s affected the field of medicine profoundly. Microbiologists quickly accepted the microscope, and their field progressed, whereas pathologists did not initially and therefore their field took a considerably longer time to develop. For this reason, in the late 1800s, microbiology, along with parasitology, was a rapidly expanding science. This change occurred especially at Johns Hopkins, where Brem trained. William Welch, MD, one of the founders of the school and hospital, was a trained microscopist and microbiologist, so he set up a pathology section that focused on microbiology and parasitology.[10,11] Due to his enthusiasm and training, medical centers across the United States were flooded with department chairs of pathology who had trained at Johns Hopkins,[12] all of whom were oriented toward the microscope and most toward the various disciplines of microbiology. Walter Reed took postgraduate courses at Johns Hopkins and did some research there when he was curator of the Army Medical Museum in Washington, DC.[13]

All of these factors must have stirred great interest in a young medical student. Further, Brem, having been a soldier in the Spanish-American War, must have seen the US Army Sanitary Commission in action and was thus made aware of the usefulness of laboratory medicine. Last, Osler, under whom Brem took his internship, had worked with MacCallum and others on a series of studies on malaria; from that it is possible to trace his exposure to the disciplines of microbiology and infectious disease. It was almost inevitable that Brem would enter some area of infectious disease or laboratory medicine, and the Canal Zone undoubtedly provided a strong drawing force, particularly with its many close ties with Johns Hopkins Medical Center. He accepted a position in the Canal Zone at Colon Hospital in 1905.

It is more difficult to explain why Zeiler entered the Canal Zone in 1906. His training did not particularly befit him for any laboratory area, nor was his medical school particularly noted for laboratory medicine. In fact, the position that he

(Myhre BA, Cremin JH: Pioneer transfusionists of Los Angeles. West J Med 1987 Mar; 146:378-380)

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received in Ancon Hospital was that of an assistant surgeon, and he initially spent his time doing clinical medicine. His son states that the motivation may have been that his father needed a job, and one was open in the Canal Zone. In 1907 Zeiler was reassigned to the Colon Hospital at the other end of the Canal Zone, where he and Brem became co-workers in doing clinical laboratory tests.

They coauthored three papers during their lifetimes: one on intestinal amebiasis, another on influenzal meningitis and the third on the use of fasting blood donors. The first two of these were based on their Canal Zone experience. In each case Brem was the senior author and, in addition, he wrote 14 other papers and coauthored one other with F.C. Watson. Although in many cases Zeiler contributed to the work, he disliked writing and, therefore, sometimes was not listed as an author of work to which he contributed (Meyer Zeiler, MD, oral communication, October 1984).

At the end of their Canal Zone experience, the physicians decided to go to Milwaukee to set up an office. This may have been at the urging of Mrs Brem, who was originally from Milwaukee. The American Medical Association's 1911 meeting, however, was being held in Los Angeles (the first time this meeting was held in the West), and en route to Milwaukee, Brem presented a paper at the meeting on typhoid vaccine therapy for typhoid carriers. Apparently he was entranced by Los Angeles and decided to establish a laboratory in that community. Later that year he set up an office in the Security Building at Fifth and Spring Streets where, before the year was finished, he was joined by Zeiler as a partner in the practice of clinical laboratory medicine. As time went on, they provided laboratory service for many of the hospitals in the downtown Los Angeles area.

Early in their practice, they began to do blood transfusions. Their first transfusion was given on April 2, 1912,[7] to a woman receiving care at Good Samaritan Hospital for pernicious anemia. In the account book in which they kept records of their office practice, there is recorded on December 18, 1912, the outpatient transfusion of 250 ml of blood of Moss type III to a patient, Mr S, from a donor, Miss F. By 1916, Brem was able to report that they had performed more than 200 transfusions using defibrinated blood, direct transfusion and citrated blood.[14] No record exists of all the individual patients or the diseases for which they were transfused, but, in general, due to the laborious nature of the procedure, only those patients with chronic anemias such as pernicious anemia or leukemia were transfused. Yet Dr M. Zeiler comments that he knows of at least one occasion when his father did go to French Hospital to transfuse several patients who had influenza during the 1918 epidemic in an effort to "pick up their resistance." A few times, trauma cases of various types were transfused, but we have no record as to the outcome of the patients. Blood transfusions were given whenever needed. Dr Zeiler tells how his father was called out of various social gatherings or from bed at night to give transfusions.

The donors used for these transfusions were usually paid. Brem's article states that they preferred truck drivers, who were usually large men with "enormous veins." These donors were ABO grouped before being added to the donor panel, and a Wassermann test was done. The donors were then called when needed. The transfusions were done usually in the office, although some were done in various local hospitals.

The method used was a variant of the Lindeman multiple-syringe technique.[5] The patient and donor were placed next to each other, a needle was placed in the antecubital vein of each and a syringe full of blood was removed from the donor. The filled syringe was then passed to the other physician, who injected the blood into a needle inserted into the vein of the patient. Blood was kept from flowing from the open needle by placing the gloved finger over the end of the needle. Dr Zeiler remembers that at the start of an operation, about 25 syringes, 20-ml size, were made available. If blood began to clot, the offending syringe was rinsed in saline until it moved freely once again. Both the donor and the recipient were sterilely draped, partly in an effort to preserve sterility and partly to preserve the anonymity of the donor and of the recipient. On at least one occasion this anonymity broke down. Dr Zeiler recalls one of his father's stories of transfusing a famous opera soprano, and at the completion of the procedure, the singer approached the donor and said in her thick German accent, "Do you know that you have just given blood for the great Madame Schumann-Heink?"

It is interesting to note that, even though sodium citrate had been found to be useful as an anticoagulant of blood, Brem and Zeiler and many others still transfused blood directly without an anticoagulant. This choice has been recently discussed by Wain.[15] Most of the transfusionists of that day believed (corroborated supposedly by statistics) that the use of citrate was almost always accompanied by a rather severe febrile reaction that was ascribed to the citrate. It was another ten years before the work of Seibert[16] showed that it was not the citrate itself that usually caused the reaction, but rather the bacterial pyrogens that remained after cleansing the reused flasks and tubing. The introduction of disposable plastic equipment largely eliminated this hazard. It is of little wonder that, if most patients experienced febrile reactions of 3°F to 5°F and these were ascribed to the citrate, there was little interest in using the incriminated anticoagulant. Another hazard with citrate that was addressed in Brem's article was the use of the 1% formula advocated by Weil.[17] It was eventually found that this concentration could be toxic and that Lewisohn's formula[18] was much better tolerated.

The unique aspect of the Brem-Zeiler transfusion procedure was their early reliance on laboratory testing. It is difficult today to perceive just how crude the methods were during those early years. Landsteiner,[19] writing in 1901, had shown the existence of three naturally occurring blood groups in humans. Work by De Castello and Sturli[20] in 1902 added the fourth group to what we now know as the ABO system. Yet Crile[4] in his 1909 book described using a simple hemolysin test in some cases and does not even mention the existence of blood groups. Hektoen in 1907 urged that blood of compatible groups should be transfused, but did not elaborate beyond that.[21] In 1908 Ottenberg listed compatibility testing as an addition to his report about a method of doing arteriovenous anastomoses, but it was not used at Mount Sinai Hospital. He writes,

> As I was in the laboratory, I offered to do the compatibility tests, but many of the surgeons did not accept the offer. They felt that since Crile had done a large series of transfusions without tests (and with only a few cases of hemolysis and no deaths) they ought to be free from interferences by the laboratory men. It took about five years of campaigning, experimenting and a few accidents to convince the medical public that blood tests before transfusion were essential.[22(p266)]

Another obstacle to crossmatching was the personal nature of blood transfusions. As has been stated previously, only a

few persons in each city performed transfusions. Most of these physicians were highly paid and very probably did not wish to share the income with others. Further, there was inadequate experience to show that safety would be increased by a nonsurgical technique. In this light, the comments of Ottenberg become particularly relevant. Crossmatching as we know it today did not gain much nationwide popularity until just before World War II.

Meanwhile, Brem and Zeiler in 1911 developed their method of blood group testing.[14] This became well enough known that it is mentioned by Ottenberg, who says, "following the suggestion of Brem of San Francisco [*sic*] it was thought sufficient to determine the group of patient and donor."[22 (p 267)] Yet, rather than a simple determination of the blood group, the method was unique and was aided somewhat by the fact that Brem had group B blood and that Zeiler had group A. Thus, they always had a set of known reagents available for typing. Basically, the blood of the patient was crossmatched with the blood of either Brem or Zeiler. By simply observing the agglutination of the erythrocytes and the serum of both persons, the blood type of the patient could be determined. Blood from a donor of the identical type was always used. Why were these physicians doing crossmatches when the medically advanced Easterners were not? Undoubtedly the major reason was that there were no other transfusionists who had vested interests in preserving the status quo and who would thus interfere.

All early records kept in the Brem-Zeiler laboratory used the Moss nomenclature for the four major blood groups. This system, described in 1910,[23] became very popular in the western United States and used Roman numerals rather than letters to indicate the blood groups. It was probably adopted by Brem and Zeiler because of Moss's association with Johns Hopkins University and because Brem was well acquainted with Moss and his work.

In their subsequent paper dated 1928,[24] Brem, Zeiler and their new associate, Hammack, discuss the occurrence of transfusion reactions and list some cases that they had observed in a series of more than 4,000 transfusions. It is interesting that many of these reactions are the same types seen today. They report, however, that 20% of their patients had a fever of more than 1°F after transfusion, which is a much higher percentage. The main purpose of their article was to show that many of the reactions they encountered could be eliminated by using fasting donors. At the end of the paper, they quote Dorn, who believed that "incompatible leukocytes" caused febrile reactions. Brem and Zeiler postulate that "digestive leukocytosis" might increase the number of leukocytes present and might give a more severe reaction. This work was not confirmed, and no one has been able to show a decrease of reactions with fasting donors. Rather, it is the unpublished experience of many that donors who have not eaten have a higher incidence of reactions, and therefore almost all blood banks today encourage a donor to eat before donating.

The time for this extremely labor-intensive and awkward procedure was drawing to a close. In 1937 Fantus established the first blood bank for the actual storing of anticoagulated blood for indirect transfusion in Cook County Hospital, Chicago.[25] World War II showed the great need for human blood and blood products in resuscitating trauma patients and stimulated the establishment throughout the world of blood banks as we know them. During that time period, direct transfusions came to an end. Today in the United States more than 10 million units of blood and blood products are transfused annually. Yet none of this might ever have happened if it had not been for this small band of physicians who spent much of their lives studying methods of doing safer and better blood transfusions.

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Mitral Valve Prolapse Syndrome—Myth or Reality?

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MITRAL VALVE PROLAPSE has been proposed as a cause of, or having significant association with, anxiety and other psychological symptoms. The concurrence of this cardiac anomaly with a wide range of psychological symptoms has been promoted by some authors to syndrome status. In this article I will review the medical literature that both suggests and refutes a clear association between mitral valve prolapse and psychiatric symptoms.

Definition of the Mitral Valve Prolapse Syndrome

Mitral valve prolapse was originally described by Reid[1] and Barlow[2] in 1961 and 1962, respectively. They defined it as auscultative findings of a nonejection click with or without a late systolic murmur, heard best at the heart's apex. Prolapse is confirmed by the classic picture seen in echocardiography (Figure 1). Several subsequent studies have suggested that symptoms of panic disorder (Table 1) are frequently associated with mitral valve prolapse.[3-5] This association between auscultative and echocardiographic signs, together with psychiatric symptoms, has come to be known as the mitral valve prolapse syndrome.

Mitral valve prolapse may be due to a number of diseases (Table 2). Because these conditions may be the origin of symptoms, which may also be features of anxiety, the mitral valve prolapse syndrome has been redefined as primary or idiopathic mitral valve prolapse associated with symptoms of panic disorder.

Studies That Support the Syndrome

Table 3 lists studies of patients referred to cardiac clinics because their physicians had discovered clicks on auscultation. The incidence of symptoms, which included atypical chest pain, palpitations and dyspnea, ranged from 70% to 80%. The methodologic problems in these studies include small population size, no controls are used, patients with primary and secondary mitral valve prolapse are grouped together and patients are preselected for being symptomatic.

Some researchers have studied psychiatric rather than cardiac clinic populations. Venkatesh examined 21 patients with panic disorder and found 7 (33%) to have mitral valve prolapse.[9] There was no control group in this study. Agoraphobia frequently develops in patients with panic disorder due to their progressively avoiding situations.[6] Kantor and co-workers examined 25 agoraphobic patients and found 11 (44%) to have mitral valve prolapse, whereas only 2 (9%) of 23 control subjects had it.[10]

Silverman and associates selected 68 consecutive patients with mitral valve prolapse from a private practice of four physicians in internal medicine.[11] For controls, 68 concurrent patients matched by age and sex to the group with mitral valve prolapse were selected. Both groups were evaluated for symptoms, which included chest pain, syncope, palpitations, dizziness and dyspnea. In all, 64 (94%) of the patients with valvular prolapse were symptomatic compared with 51 (75%) of the control subjects. Palpitations were present in 48 (71%) members of the group with valvular prolapse, compared with 23 (34%) of the controls. This study failed to distinguish between primary and secondary mitral valve prolapse.

Evidence Against the Mitral Valve Prolapse Syndrome

Hartman and colleagues studied 141 patients with mitral valve prolapse and found 22 (16%) to have panic disorder.[12] This compares with the general population rate of 4% to 7%.[13] A total of 103 adult relatives of 26 of the patients with mitral valve prolapse were studied and 33 (32%) had mitral valve prolapse. Of these, one (3%) had panic disorder. Two (3%) of the remaining relatives without mitral valve prolapse had panic disorder. These results show an expected high inheritance rate of valvular prolapse,[7] but fail to show any higher association of panic disorder in the relative group than in the general populations.

Uretsky studied 972 consecutive patients presenting to an adult general medical practice.[14] He broke this population down into two groups: patients with mitral valve prolapse (45) and patients without it (742 with medical disease and 184 "healthy"). He compared the prevalence of both atypical chest pain and neuropsychiatric symptoms in these two groups. Initial comparisons showed a significantly higher rate of symptoms for the patients with the prolapse.

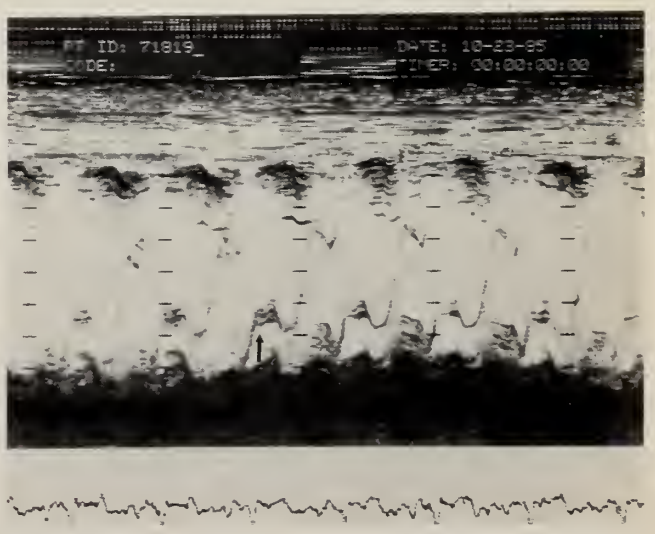

Figure 1.—Arrow indicates echocardiographic evidence of mitral valve prolapse (courtesy of Department of Cardiology, Northridge Hospital, Northridge, Calif).

(Pollack RD: Mitral valve prolapse syndrome—Myth or reality? West J Med 1987 Mar; 146:381-382)

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The same abnormally high rate is found, however, in the subgroup of patients without mitral valve prolapse who were called "healthy." Uretsky concluded that these data suggest "a coincidence of a common syndrome with frequently occurring symptoms rather than cause and effect."[14]

The largest study examining this issue is the Framingham study.[15] Nearly 3,000 people in the general population were examined, and 208 were found to have echocardiographic evidence of mitral valve prolapse (an incidence of 6%). Subjects with and without prolapse were compared for symptoms of chest pain and dyspnea and no statistically significant difference between the two groups was found.

Discussion

Syndrome means "a running together." Signs and symptoms occur so frequently together as to be statistically significant. The research suggesting a mitral valve prolapse syndrome suffers in two major areas of design: (1) the low population sizes studied and (2) selection bias. The research that fails to show any link between psychiatric symptoms and mitral valve prolapse effectively deals with both of these variables. The study by Hartman and co-workers deals with selection bias by examining the families of patients with the prolapse.[12] Uretsky compares these patients with another preselected symptomatic group, "healthy" patients. The Framingham study removes the "patient" preselection variable altogether by doing a random sampling of a population.

The evidence presented here suggests that a syndrome linking mitral valve prolapse and psychiatric symptoms has not been established. Barlow and Pocock come close to concurring with this view.[16] In 1979 they agreed with Motulsky's conclusion that "for every patient with symptomatic mitral valve prolapse . . . there are hundreds of asymptomatic persons."[17] Barlow and Pocock recommend that asymptomatic patients who have mitral valve prolapse be left alone to minimize iatrogenic anxiety. They also state that symptomatic patients should be treated only when there is evidence of a potentially malignant arrhythmia.

Mitral valve prolapse syndrome continues to be cited in the medical literature as an explanation for various anxiety states.[18-21] These articles do not mention the research presented here that fails to support this view. This additional information should be considered to minimize the risk of iatrogenic disease and so that physicians will not be limited in their attempts to treat an anxious patient.

TABLE 1.—*Symptoms of Panic Disorder**

Dyspnea
Palpitations
Chest pain or discomfort
Choking or smothering sensation
Dizziness, vertigo or unsteady feelings
Feelings of unreality
Paresthesias (tingling in hands or feet)
Hot and cold flashes
Sweating
Faintness
Trembling or shaking

*From American Psychiatric Association.[6]

TABLE 2.—*Some Conditions That Cause or Are Closely Associated With Mitral Valve Prolapse**

Marfan's syndrome
Rheumatic endocarditis
Occlusive coronary artery disease
Congestive cardiomyopathy
Idiopathic hypertrophic subaortic stenosis
Myocarditis
Mitral valve operation
Trauma
Left ventricular aneurysm
Wolff-Parkinson-White syndrome
Systemic lupus erythematosus

*From Barlow and Pocock.[7]

TABLE 3.—*Cardiac Clinic Patients With Mitral Valve Syndrome*

Study	*Population Size, Number*	*Patients Symptomatic, Percent*
Hancock and Cohn, 1966[3]	40	75
Fontana et al, 1970[4]	30	70
Jeresaty, 1973[5]	100	80
Malcolm et al, 1976[8]	85	80

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(Continued from Page 310)

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March 20—**Diabetes and Nutrition Update** (Sponsor: UUMC). Fri. Univ of Utah, Salt Lake City. 8 hrs. Contact: (801) 581-5809.

March 26-28—**Neurology for the Practitioner** (Sponsor: UUMC). Thurs-Sat. Salt Lake City. 15 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

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WASHINGTON

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Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 18—**New Directions in Gynecologic Research.** Seattle. Wed. U/W Health Sciences. Contact: U/W.

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March 30-April 10—**Rehabilitation Medical Review.** Seattle. Mon-Fri. Stouffer Madison Hotel. Contact: U/W.

April 15—**Anorectal.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

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U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 623-4801.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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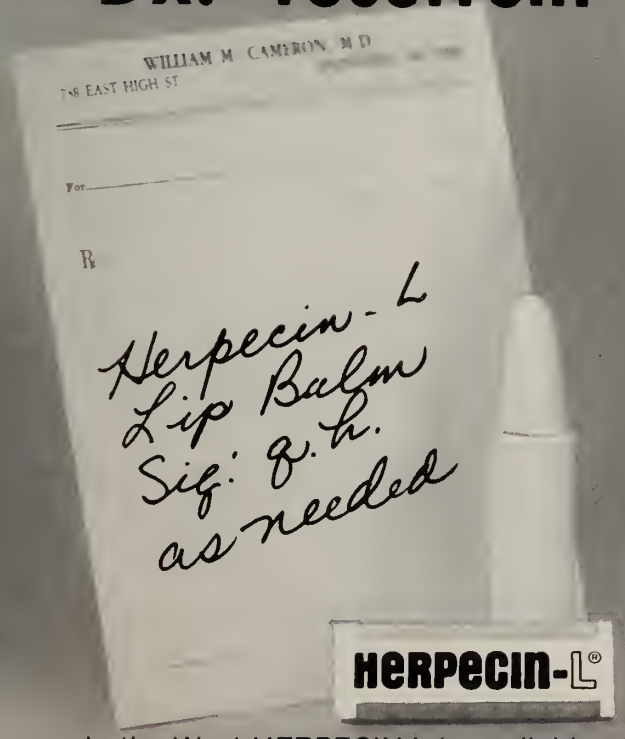

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In Memoriam

California Medical Association

BERKERY, EMMET M. Died Nov 8, 1986, aged 69. Graduate of State University of New York Downstate, Brooklyn, 1943. Licensed in California in 1949. Dr Berkery was a member of the Los Angeles County Medical Association.

BEST, ELBRIDGE J., San Francisco. Died Dec 12, 1986, aged 99. Graduate of University of California, San Francisco, 1911. Licensed in California in 1911. Dr Best was a member of the San Francisco Medical Society.

BROADLEY, PAUL H., San Diego. Died Nov 9, 1986, aged 54. Graduate of Tufts University School of Medicine, Boston, 1957. Licensed in California in 1967. Dr Broadley was a member of the San Diego County Medical Society.

CHERRY, CLIFFORD B., Los Angeles. Died Dec 8, 1986, aged 76. Graduate of Stanford University, Stanford, California, 1935. Licensed in California in 1935. Dr Cherry was a member of the Los Angeles County Medical Association.

CRARY, GERALD C., Santa Cruz. Died Dec 9, 1986, aged 56. Graduate of University of Oregon School of Medicine, Portland, 1955. Licensed in California in 1956. Dr Crary was a member of the Santa Cruz County Medical Society.

FELDMAN, JACOB F., Los Angeles. Died Nov 15, 1986, aged 89. Graduate of McGill University Faculty of Medicine, Montreal, 1923. Licensed in California in 1923. Dr Feldman was a member of the Los Angeles County Medical Association.

FISHMAN, HARVEY C. Died Sep 27, 1986, aged 75. Graduate of University of Manitoba, Winnipeg, 1937. Licensed in California in 1948. Dr Fishman was a member of the Los Angeles County Medical Association.

HOLDSWORTH, MODE J., Los Gatos. Died Oct 27, 1986, aged 84. Graduate of University of Michigan, Ann Arbor, 1925. Dr Holdsworth was a member of the Santa Clara County Medical Society.

KENNEDY, CHARLES R. Died Oct 28, 1986, aged 88. Graduate of University of Colorado School of Medicine, Denver, 1930. Licensed in California in 1930. Dr Kennedy was a member of the San Luis Obispo County Medical Society.

LAWLER, WILLIAM H., SR, Salinas. Died Nov 23, 1986, aged 86. Graduate of Stanford University, Stanford, California, 1928. Licensed in California in 1928. Dr Lawler was a member of the Monterey County Medical Society.

MACCALLUM, DANIEL B. Died Nov 12, 1986, aged 88. Graduate of Rush Medical College, Chicago, 1926. Licensed in California in 1927. Dr MacCallum was a member of the Los Angeles County Medical Association.

Montana Medical Association

MCGREGOR, ROBERT J., Great Falls. Died Jan 1987, aged 73. Graduate of University of Iowa College of Medicine, Iowa City, 1937. Dr McGregor was a member of the Cascade County Medical Society.

New Mexico Medical Society

RICE, LUCIEN G., Jr, Albuquerque. Died Feb 5, 1987, aged 78. Graduate of Cornell Medical College, New York, 1935. Licensed in New Mexico in 1938. Dr Rice was a member of the Greater Albuquerque Medical Association.

Utah State Medical Association

COOK, JOHN H., Salt Lake City. Died Oct 31, 1986, aged 58. Graduate of University of Utah. Licensed in Utah in 1957. Dr Cook was a member of the Salt Lake County Medical Society.

DAINES, LAURA L., Salt Lake City. Died Oct 30, 1986, aged 73. Graduate of University of California. Licensed in Utah in 1947. Dr Daines was a member of the Salt Lake County Medical Society.

RICH, CHARLES O., Salt Lake City. Died Nov 15, 1986, aged 88. Graduate of Washington University College of Medicine, St Louis. Dr Rich was a member of the Salt Lake County Medical Society.

WINTROBE, MAXWELL M., Salt Lake City. Died Dec 9, 1986, aged 85. Graduate of University of Manitoba, Winnipeg. Dr Wintrobe was a member of the Salt Lake County Medical Society.

CONTINUING MEDICAL EDUCATION

(Continued from Page 385)

April 17—**Basic Monitoring Laboratory.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

April 24-25—**Benton-Franklin County Medical Society's 3rd Annual CME Seminar.** Richland. Fri-Sat. Holiday Inn. Contact: A. K. Sen, MD, (509) 783-4186.

April 25—**Mason Clinic Day.** Seattle. Sat. Virginia Mason Medical Center. Contact: VMMC.

May 1—**Topics in Pulmonary Medicine: Obstructive Airflow Disease Treatment.** Seattle. Fri. Virginia Mason Medical Center. Contact: VMMC.

May 8—**Current Issues in Asbestos Control.** Seattle. Fri. NW Center for Occupational Health and Safety. Contact: U/W Dept of Environmental Health, SC-34, Seattle 98195. (206) 543-1069.

May 13—**Neonatal.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

May 14-15—**Clinical Microbiology.** Seattle. Thurs-Fri. Contact: U/W.

May 20—**Management of Benign and Malignant Breast Disease.** Seattle. Wed. U/W Health Sciences. Contact: U/W.

May 27—**Dermatology.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

May 28-29—**Workers Compensation Update.** Seattle. Thurs-Fri. NW Center for Occupational Health and Safety. Contact U/W.

June 3—**Flexible Sigmoidoscopy III or IV.** Seattle. Wed. Gould Auditorium, Northwest Hospital. Contact: (206) 364-0500, #1621.

June 17-19—**Family Violence.** Seattle. Wed-Fri. Kane Hall, U/W. Contact: U/W.

June 25-26—**Infectious Diseases.** Seattle. Thurs-Fri. Holiday Inn Crowne Plaza. Contact: (206) 364-0500, #1621.

July 19-23—**Reducing Risks From Environmental Chemicals Through Biotechnology.** Seattle. Sun-Thurs. NW Center for Occupational Health and Safety. Contact: U/W.

July 24-26—**WSSA: Seafair IX Regional Anesthesia.** Seattle. Fri-Sun. Virginia Mason Medical Center. Contact: VMMC.

July 27-31—**The Pathology of Lung Cancer.** Seattle. Mon-Fri. Virginia Mason Medical Center. Contact: VMMC.

WYOMING

June 25-29—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Mon. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

June 28-July 2—**Update on General Pediatrics.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152.

July 5-9—**Sports Medicine Update 1987.** University of Nebraska College of Medicine at Jackson Hole Racquet Club, Jackson. Sun-Thurs. Contact: Brenda Ram, Center for Continuing Education, Univ of Nebraska Medical Center, 42nd and Dewey Ave, Omaha, NE 68105. (402) 559-4152. ◆

(Continued from Page 386)

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GASTROENTEROLOGIST—BC/BE for multispecialty group downtown San Francisco. Send CV and references to: 757 Sutter Medical Clinic, Ste. 100, San Francisco, CA 94109; (415) 391-9292.

ORTHOPAEDIC STAFF PHYSICIAN. Busy, university-affiliated, hospital-based Orthopaedic practice seeking MD who has two years of postgraduate training. Will take call, assist in OR. Experience and/or interest in Orthopaedic surgery highly preferable. Start July 1, 1987. Send résumé: Department of Orthopaedics, Pacific Medical Center, 1200 12th Ave. South, Seattle, WA 98144.

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DIRECTOR, FAMILY PRACTICE RESIDENCY IN BOISE, IDAHO, 18 resident program affiliated with University of Washington. Board certification, teaching experience, private practice and administrative skills required. Academic appointment, salary and benefit package commensurate with experience. Application deadline April 15, 1987. Contact John Mohr, MD, Director, Family Practice Residency of Idaho, 777 N. Raymond, Boise, ID 83704.

PEDIATRICIAN—East Bay multispecialty group is pleased to announce the opening of a position for a Board eligible/certified Pediatrician. Established practice with a diversified patient population. Possible equity position after short tenure. Competitive starting salary and benefits. Contact Alan Steinbach, MD, Medical Director at: 400-29th St., Ste. 512, Oakland, CA 94611; (415) 893-5600.

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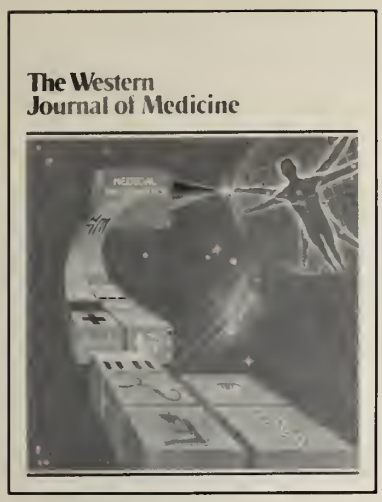

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1987, Pointe South Mountain, Phoenix.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 863-5522. Annual Meeting: March 6-11, 1987, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1987: Date and place to be announced.

Hawaii Medical Association—320 Ward Ave, Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1987: Date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 27-August 2, 1987, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Interim Meeting: April 3-4, 1987, Colonial Inn, Helena.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 30-May 3, 1987, Ormsby House, Carson City.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 6-8, 1987, Clarion Four Seasons, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 3-4, 1987, Salishan Lodge, Lincoln City.

Utah State Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1987: Date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1987: Date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 25-29, 1987, Jackson Lake Lodge, Moran.

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ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

MICROBIOLOGY The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis Ceftriaxone has a high degree of stability in the presence of beta lactamases, both penicillinases and cephalosporinases, of gram-negative and gram positive bacteria Ceftriaxone is usually active against the following microorganisms *in vitro* and in clinical infections (see Indications and Usage)

GRAM NEGATIVE AEROBES Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), *H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *Neisseria gonorrhoeae* (including penicillinase and nonpenicillinase producing strains), *Neisseria meningitidis, Proteus mirabilis, Proteus vulgaris, Morganella morganii* and *Serratia marcescens*

Note Many strains of the above organisms that are multiply resistant to other antibiotics, *e g* penicillins, cephalosporins and aminoglycosides, are susceptible to ceftriaxone sodium

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa*

GRAM POSITIVE AEROBES Staphylococcus aureus (including penicillinase-producing strains) and *Staphylococcus epidermidis* (Note methicillin resistant staphylococci are resistant to cephalosporins, including ceftriaxone), *Streptococcus pyogenes* (Group A beta hemolytic streptococci), *Streptococcus agalactiae* (Group B streptococci) and *Streptococcus pneumoniae* (Note Most strains of enterococci, *Streptococcus faecalis* and Group D streptococci are resistant)

Ceftriaxone also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance is unknown

GRAM NEGATIVE AEROBES Citrobacter freundii, Citrobacter diversus, Providencia species (including *Providencia rettgeri*), *Salmonella* species (including *S typhi*), *Shigella* species and *Acinetobacter calcoaceticus*

ANAEROBES Bacteroides species, *Clostridium* species (Note most strains of *C difficile* are resistant)

SUSCEPTIBILITY TESTING Standard susceptibility disk method Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility One such procedure (Bauer AW, Kirby WMM, Sherris JC, Turck M Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol* 45 493-496, 1966, Standardized Disk Susceptibility Test, *Federal Register* 39 19182-19184, 1974, National Committee for Clinical Laboratory Standards, Approved Standard ASM 2, Performance Standards for Antimicrobial Disk Susceptibility Tests, July 1975) has been recommended for use with disks to test susceptibility to ceftriaxone

Laboratory results of the standardized single-disk susceptibility test using a 30-mcg ceftriaxone disk should be interpreted according to the following three criteria

1 Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy
2 Organisms that produce zones of 14 to 17 mm are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g, urine), in which high antibiotic levels are attained
3 Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected

Organisms should be tested with the ceftriaxone disk, since ceftriaxone has been shown by *in vitro* tests to be active against certain strains found resistant to cephalosporin class disks

Organisms having zones of less than 18 mm around the cephalothin disk are not necessarily of intermediate susceptibility or resistant to ceftriaxone

Standardized procedures require use of control organisms The 30-mcg ceftriaxone disk should give zone diameters between 29 and 35 mm, 22 and 28 mm and 17 and 23 mm for the reference strains *E coli* ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853, respectively

DILUTION TECHNIQUES Based on the pharmacokinetic profile of ceftriaxone, a bacterial isolate may be considered susceptible if the MIC value for ceftriaxone is not more than 16 mcg/ml Organisms are considered resistant to ceftriaxone if the MIC is equal to or greater than 64 mcg/ml Organisms having an MIC value of less than 64 mcg/ml, but greater than 16 mcg/ml, are expected to be susceptible if a high dosage (not to exceed 4 gm per day) is used or if the infection is confined to tissues and fluids (e g, urine), in which high antibiotic levels are attained

E coli ATCC 25922, *S aureus* ATCC 25923 and *P aeruginosa* ATCC 27853 are also the recommended reference strains for controlling ceftriaxone dilution tests Greater than 95% of MICs for the *E coli* strain should fall within the range of 0 016 to 0 5 mcg/ml The range for the *S aureus* strain should be 1 to 2 mcg/ml, while for the *P aeruginosa* strain the range should be 8 to 64 mcg/ml

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

PROPHYLAXIS The administration of a single dose of ceftriaxone preoperatively may reduce the incidence of postoperative infections in patients undergoing coronary artery bypass surgery

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

ROCEPHIN® (ceftriaxone sodium/Roche)

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category *B* Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, glycosuria, hematuria, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams) given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered ½ to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function however, blood levels should be monitored in patients with severe renal impairment (e g, dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1962 01)
Vials containing 500 mg equivalent of ceftriaxone Boxes of 10 (NDC 0004 1963 01)
Vials containing 1 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1964 01)
Piggyback bottles containing 1 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1964 03)
Vials containing 2 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1965 01)
Piggyback bottles containing 2 gm equivalent of ceftriaxone Boxes of 10 (NDC 0004 1965 03)
Bulk pharmacy containers, containing 10 gm equivalent of ceftriaxone Boxes of 1 (NDC 0004 1971 01)
NOT FOR DIRECT ADMINISTRATION

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

ROCHE®

References:

1. Data on file, Hoffmann-La Roche Inc.
2. Patel IH, Kaplan SA. *Am J Med 77*:17-25, Oct 19, 1984
3. Richards DM, *et al: Drugs 27*:469-527, 1984.
4. Cleeland R, Squires E: *Am J Med 77*:3-11, Oct 19, 1984
5. Tanner DJ, Nazarian MQ: *Am J Med 77*:104-111, Oct 19, 1984.

Mean,

Powerful against susceptible pathogens.*

lean &

Easy on tight budgets.

clean.

Gentle to patients (generally well tolerated).

The one antimicrobial that
belongs on every formulary.

Once-a-day

Rocephin® ROCHE IV·IM

ceftriaxone sodium/Roche

* ROCEPHIN is indicated in the following infections: bacterial septicemia, bone and joint, intra-abdominal, lower respiratory tract, skin and skin structure, urinary tract, bacterial meningitis and gonorrhea. Please see summary of product information on adjacent page for indicated susceptible organisms.

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Please see adjacent page for summary of product information.